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Acta Pædiatrica

Vol. 46 · May 1957 · No 3

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Subscription Price 50 Swedish kronor. Single copies 10 Swedish kronor.
Published by ALMQVIST & WIKSELLS BOKTRYCKERI AB, Uppsala, Sweden.

Bilaga medföljer

ACTA PÆDIATRICA

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Acta Pædiatrica 46: 215—231. May 1957

Linné as Pediatrician

by TELEMAK FREDBÄRJ

During 37 years (1741–1778) Linné was professor at the medical faculty of the University of Uppsala and lectured and examined in semiotics, dietetics, materia medica and natural history while the other professor of the faculty, NILS ROSÉN, had charge of anatomy, physiology and practical medicine. Seen with our eyes Linné had to teach in surprisingly many subjects: pathology, chemistry, pharmacology; medicine, pediatrics, epidemiology, surgery, gynecology, hygiene; botanics, zoology and mineralogy. Within all these subjects he gradually documented himself as well as in anatomy, physiology, veterinary medicine, agriculture and mining science. His posthumous manuscripts, kept in the Linnean Society in London, contain several thousand pages, most of them not published. He was also a remarkably active member of the Academic Consistorium, he was the Rector of the University for three different periods and Inspector of the "Nation" of Småland in over 30 years (since 1744 when he succeeded Anders Celsius). He was one of the founders of the Royal Swedish Academy of Science and its first president and he was one of the promoters and the collaborators in the first Swedish Pharmacopoeia (1775).

He corresponded with the most prominent men of science of his time (about 1,500 letters written by him are known; 10 volumes of his correspondance have been published but just as many remain unpublished). It is difficult to understand that one man could carry on such a heavy program, especially as he did not have any of the technical equipments of our time at his disposal. One of his mottos was a'so "*Nulla dies sine linea*" (no day without a line). To write about Linné as pediatrician is therefore only to treat a small—and hitherto overlooked—part of his gigantic production.

First some words about the general medical authorship of Linné.[1]

During his lifetime he published three medical books: *Genera morborum*, *Materia medica* and *Clavis medicinae*. On the occasion of the Linné Jubilee

To the 250 anniversary of the birth of CARL VON LINNÉ.

[1] The archiater professor OTTO HJELT has in his book CARL VON LINNÉ as Physician and Medical Author (Uppsala 1907) in more detail discussed this subject.

in 1907 his *Lachesis naturalis* moreover was printed constituting his lectures in dietetics. Furthermore he published not less than 85 medical theses which according to the custom of that time usually were written by Linné himself as Preses and not by the respondent. Finally he has written several medical articles in the Proceedings of the Academy of Science and in the Almanacs.

In *Genera morborum* (1763) Linné attempts to classify systematically the known diseases as described by SYDENHAM, BOERHAAVE, HOFFMANN and others, following the same principle as he had used in *Systema Naturae*, i.e. in classes, orders, families and species. His colleague Sauvages in Montpellier, with whom he corresponded for several decades, had published in 1731 a book "Nouvelles classes des maladies", which Linné now extended and improved. However, because the etiology and pathological anatomy of the majority of diseases were unknown and a basic principle of classification was lacking, Linné was guided only by the symptoms and these were sometimes mixed with the diseases themselves and this book is therefore principally of interest as a compendium of the contemporary clinical knowledge.

Materia medica (1772) comprises medical treatment as it was developed during Linné's time. The book opens with 31 rules mostly compounded by older authors but apparently in parts from Linné's own experience. Among other things he criticized the polypharmacy and says: "Those who describe drugs with long formulas sin either from deceit or from ignorance." The book which is arranged according to his *Systema Naturae* gives an account of the drugs derived from the three domains of nature which Linné considers essential in the art of treatment. For each drug he tables its synonyms, its origin, its pharmacological effect and its use, and he describes the compounds of which they are a part. Astrology and signature doctrine (Paracelsus), which dominated the old systems of pharmacology, was considered as superstition by Linné. He rejected therefore many old drugs and introduced in their place several new ones, some of which still remain officinal to-day. Already 25 years previously (*Vires plantarum* 1747) he had expressed the opinion that plants belonging to the same family, order or class correspond in their medical effects. The *vires* (powers) of the plants was one of the favourite subjects of Linné. It is considered that Linné was the founder of scientific pharmacy.

Clavis medicinae (1766) contains the summary of Linné's medical opinions. It is a book written in tabular form which is difficult to read and which according to him, "requires the age of a generation before it can be understood by the most learned man". As an example it may be briefly mentioned that Linné considered that the body of man as well as that of the plants consists of two different substances: the cortex (*corticale vitale*), "the exterior key" which comes from the father and produces skeleton, muscles, blood and viscera, and the medulla (*medullare animale*), "the interior key" that comes from the mother and corresponds to the brain and the nervous system. Diseases are mainly due to a wrong conduct of life. The drugs are either tasting (*sapida*) which influence the cortex or smelling (*olida*) which influence the medulla.

Lachesis naturalis treats the health of the body and the mind in various ages also during childhood. It gives vivid and sometimes striking examples from his own time and it contains also much of the life philosophy of Linné. These lectures on dietetics drew large audiences also from beyond the circle of medical students and because of his popular, provincial humour (Småland) they were often accompanied by outbursts of laughter in the audience.

The *dissertations* are, however, the most prominent medical publications of Linné. In these we find ideas and opinions that show how far in advance of his time he was in some matters.

Already in an article written in 1750 he postulated the existence of invisible disease agents when he wrote: "It is strange that we human beings prefer to disregard the smallest things and that we often react critically when someone 'splits a hair' and quarrels about trifles. However, if we more closely ponder such matters we might learn that the smallest things produce the greatest effects in nature and in general life. This may also be true with small-pox, measles, dysentery and syphilis, yea even plague can be produced by the most tiney vermins." In the dissertations *Exanthemata viva* (1757) and *Mundus invisibilis* (1767) he further develops his theory about *animalcula viva* (living small animals) and he considers these to be the origin also of whooping-cough, malaria, consumption and leprosy. The modes of transmission he believes to be by way of the lungs by respiration, by the throat and the stomach by deglutition and by the skin by contact. "According to the laws of nature it is apparent that the smaller an animal is, the more numerous progeny does it produce. Therefore we believe that one or two of these small insects may be sufficient to produce within short time offsprings of such numbers that the body becomes totally inundated by them." He holds that these living things are the cause of all exanthematous diseases that so far have eluded detection because of the difficulty to make careful observations. However, he contends that "our successors possessing greater skill than us will detect these small animals in much more artful ways than we believe or dare to anticipate, because nowhere is nature more complete and artful than in its smallest things"—a sentence that he has culled from the publications of the famous English scientist Boyle.

The microscope had been considerably improved essentially by Leeuwenhoek and had opened new possibilities which also Linné personally envisaged.[1] He suggests that somebody suffering from syphilis or gonorrhea experimentally may try to investigate if his sperm contains any small animals. To his friend Bäck he recommends in a letter (1748) to examine diligently pus from small-pox patients by means of good microscopes in order to detect "vermins". In *Mundus invisibilis* he writes: "It is not surprising if these small animals, which in size are 100 times smaller than a dust particle dancing in the sunshine, may be discharged into the air, scattered everywhere and be seeded out anywhere. It is possible that the smallest animals produce greater ravages than the biggest ones; it is also possible that they may kill more people than all wars."

The processes of fermentation and putrefaction are considered by Linné to be of the same kind and depending on living substances. Already in his "Journey in Skåne" (1751) he writes: "Putrefaction and fermentation are not altogether as different as physicians usually have believed" and later on he states: "Let us consider if all fermentation finally doesn't turn out to be living particles altogether."

Linné predicted not only modern bacteriology but also geographic pathology because he discoursed in several publications about the incidence of different diseases in various countries and sundry parts of one country which he correlated with diet, climate and soil.

One may generally characterize Linné as medical author by saying that he partly was philosophically speculative, embarrassed by an old ballast, partly empiric and leaning upon his own observations as well as those of

[1] The microscope of Linné is kept in the Linnéan Museum of Uppsala.

others, partly experimental and looking for new approaches, partly intuitive, divining future developments.

Pediatrics did not attain the position as a separate discipline in Sweden until 1845,[1] but the diseases of children as well as their care and breeding must of course have interested Linné as an integral part of medicine. One observes also in several of his publications and notably in *Lachesis* and the dissertations pediatric observations and reflections that show Linné's faculty of alert observation and original thinking, sometimes of course coloured by the theories of his time or by old prejudices. He stressed that the child was a growing organism which should not be regarded as a miniature adult being. In his dissertation *Instructio peregrinatoris* (1759) Linné proposes that travelling naturalists should observe and note down among other things the incidence of diseases, their popular treatments and lay medicaments. For this purpose he sets forth two questions as guiding rule: "How are the children reared? How are their actions determined by their mental attitudes?" By this same procedure he had conducted his own Swedish travels and among his notations we find repeatedly references about children.

"The basic foundation of human life is laid at the conception", says Linné in *Fundamenta valetudinis* (the foundations of health) and in this wording he attempts to stress the importance of heredity for the future health. The same idea is stressed in another manner in *Lachesis*: "Happy is the man born of healthy parents in the strongest oestrus." The conception of man, of his birth and death were items which preoccupied Linné philosophically throughout his life.

Linné considered the sexual instinct and its research as part of medicine and he probably should be regarded as our first sexual pathologist. In his lectures on dietetics he talked about the anatomy and the functions of the sexual organs and in his system of diseases he also mentioned several sexual anomalies which unfortunately offended some prudish people, among others the queen. When he lectures on *Venus* (love) he says introductorily: "This matter is the most difficult to discuss in public, not for the subject itself but because of the audience, since to those with inhibitions from youth it sounds as something strange, but one should listen to these things with common sense and *castis auribus* (with chaste ears). An anatomist is not ashamed to talk about penis or vulva more than about nose and mouth because all these organs are shaped at the same time. — The genitals of the plants we look upon with delight, those of animals with shame and our own with unbecoming thoughts."

[1] At the Caroline Institute when FREDR. THEOD. BERG at the Foundling Hospital became the first professor of pediatrics.

The process of conception was for Linné one of the great wonders of nature and he says in another lecture:[1] "*Conceptio est miraculum mundi* and the greatest work that The Creator has made in nature; how two human beings could reproduce themselves into another human being that is similar to its own organs and parts, how *ovum* is generated, how life is transmitted, how the *foecundatio* occurs." For Linné the *ovum* was the most important thing at the conception and Harvey's famous sentence "*Omne vivum ex ovo*" he made to his own; he even included an *ovum* in his nobleman's coat-of-arms. He was critical of the spermatozoas (*vermiculi seminales*) that had been discovered by Ham in 1677 and more extensively studied by Leeuwenhoek. They had as a matter of fact been demonstrated for him in Leyden 1737 but Linné considered them to be lifeless things and their movement depending upon the heat of the seminal fluid (*Sponsalia plantarum* 1746, *Generatio ambigena* 1759).

In the theses *Odores medicamentorum* (1752), *Fundamenta valetudinis* (1756), *Diaeta aetatis humana* (1764), *Metarmorphosis humana* (1767) and in *Lachesis naturalis* Linné describes the somatic and mental development and offers a continuous hygiene for the human life which following Hippokrates he divides into seven-year periods. The childhood is in these publications treated in special chapters.

Infantia (infants and toddlers) comprises according to Linné the ages from birth to the second dentition.

He gives information about the fetal period at the termination of which the child reposes in its mother's womb with knees and hands bent towards the face, with large head and open mouth, and with the bones of the cranium separated at the sutures.

At birth the head presents itself first and because it is broader than the shoulders, the rest of the body is readily delivered. "The fetus now starts inhaling the lifegiving air and its very first expression upon facing the world is to cry aloud. This weak fetus opens its eyes which are bereft of sight due to Haller's membrane, neither does it comprehend any sounds because the ears are plugged, neither does it smell anything because both the nose and the sinus of the maxillary bones are plugged. Its bones are cartilaginous, the body fleshy and soft, the veins more numerous, the nerves bigger and the sensitivity therefore greater. The fluid parts generally surpass the solid ones and the consequence is sensitivity and delicateness."

Linné finds it natural and good that the newborn child should be bathed and cleaned but not by means of soap and other irritating things. He warns against the bad custom of rich people who in order to be "different" wash

[1] Published in F. Bryk, Linné as Sexualist, Stockholm 1951.

their children in wine, because wine when heated easily turns acid, i.e. sharp, and therefore is not tolerated by the child's delicate skin. He also disapproves of the habit of bringing the newborn infant during the chilly winterseason into the unheated church to be christened with ice-cold water. He adds: "Many springs are sprung in the hardening."

Linné occasionally looks upon the first years of life as a separate age-period, *Lactescentia*, or the milk age.[1] This age-period is characterized by almost continuous sleep, bad heat-regulation, sweating, hiccoughing after eating, babbling, innocence and simplicity. The first smile comes after the 40th day, he quotes after Plinius.

Then follows the most important matter of all: the feeding of the infant. On this subject Linné has written a special thesis, *Nutrix noverca* (the wet-nurse as a stepmother) 1752. Because this thesis can be regarded as purely pediatric it is abstracted here. It was published 12 years before NILS ROSÉN's well-known book "Informations about Diseases of Children", which in the chapter On Wet-Nurses roughly refers to Linné.

In the introduction the author speaks about the shortcomings of the time to import from southerly countries, especially France, habits regarding food, drink and clothing. The most dangerous of them all is the idea that the mothers should not give their own breastmilk to their children. "We have scarcely been expelled from our mother's womb before we fall victims to a dangerous custom, which even denies us what nature has intended to give us, breastmilk, and this is highly imprudent; neither the whales nor the big lionesses or the tigresses deny their newborns their breastmilk."

Linné then describes the colostrum, which he considers is especially valuable for the newborn infant because it helps to express the meconium, which if it is retained may give rise to diseases.[2] When the normal milk secretion starts later on, "the infant gets the best imaginable food, easy to swallow, free from all that is irritating, excellently nourishing and easily digestible". Linné quotes as example on substances that are transferred from the mother to the breastmilk: absinth imparts a bitter taste to the milk, saffron a yellow colour, onion its special odour; some drugs also are transferred, especially laxantia, likewise the mother's or the wet-nurse's bodily and mentally characteristics.[3] Here Linné is a child of the time in which he lives —a period that should last for more than one hundred years.

[1] In one of the dissertations (*Metamorph. humana*) he calls this age period *Foetus*, the age from birth to the closing of the big fontanel.

[2] This conception about the laxative effect of colostrum is derived from Aristoteles.

[3] When Linné writes in his Gotland's Journey about his childhood garden: "My mother's milk inflamed my mind with an unquenched love for plants", it is not a nice allusion he intends to convey but he literally believed it.

He then talks about impediments to the mother's lactation and he mentions syphilis, consumption, general weakness, agalactia and hypogalactia, inverted pipples, diseases in the breast. These are the only indications that Linné accepts for the use of wet-nurses. He warns against the pretexts of mothers to be free from nursing their infants and he writes: "They dupe us by saying 1. their milk is not sufficient, 2. they become weak by being bereft the juice that was intended as a nourishment to themselves, 3. they cannot take care of their infant in an adequate way because they at the same time have a tough time with their ordinary housework, 4. they have to deny the husband his sexual pleasure" (Linné believed that the women similar to the quadruped female animals go into "heat" as soon as the weaning has ceased). He stresses that milk production can develop and that a real lack of milk cannot be demonstrated until at least 8 days have elapsed. An inhibited nursing can be restored if for instance mothers after several difficult changes of bad wet-nurses become dissatisfied and finally are forced to give breastmilk themselves; during this time their breasts may even give a richer milksupply than earlier. In addition he emphasizes how many delicate women during the nursing period flourish and are restored to health. At the same time he admits the nuisance of the lactation in some cases, for instance the dripping from the nipples, pains in the breasts, soreness of the nipples, mastitis. He also warns of one consequence of inhibited breastfeeding: cancer mammae. "Therefore women of noble birth more often have cancer than the farmers' women," he says.

The next chapter could be called "warning for wet-nurses". By wet-nursing the child is bereft the advantage of the first day's colostrum. Because the wet-nurses generally come from the economically poor classes, they are forced to leave their own infants; here one feels the sympathy of Linné for the infant that has been bereft of its own mother's breast milk. Further the character of the wet-nurse is transferred with the milk to the child. He says: "Accustomed to solid and simple food and hard work ever since childhood the wet-nurses begin a pleasant and inactive indoor life, they eat much, they drink heavily and therefore they become plethoric, lustful and finally suffer from melancholia." Even anger in the wet-nurse is dangerous because the child through the milk may get abdominal pains, vomitings, even convulsions.[1] If the wet-nurse is strabistic and grim or attractive and merry, the child turns the same. With historical examples Linné attempts to show the truth of his opinion: Nero had a wet-nurse that was a drunkard and therefore he was addicted all his life to drinking; the wet-nurse of Caligula smeared her breast with blood in order to get the infant to suck the nipples more willingly with the result that as an adult he

[1] Rosén von Rosenstein held the same opinion.

became enormously blood-thirsty; the old heroes had fed their infant boys with lioness' milk in order to make them brave.—The risk of transmitting a common cold from the wet-nurse to the child is stressed. Most dangerous is, however, if she is afflicted with syphilis. Linné tells about such a case from his own practice when a syphilitic wet-nurse infected a child which later infected its own mother who in turn infected her husband. When the disease of the wet-nurse was detected she was dismissed, but then she served in the house of a baron and infected his child that died. Therefore Linné says that if it is absolutely necessary to engage a wet-nurse, one should choose the best one available and she must be examined and approved by a physician.—Further he states that the wet-nurse has never the same love for the child as the mother, and that even she may beat it so severely that it becomes crippled or hunchbacked, or she frightens it so that the child gets nightmares or she suffocates it during the sleep by her carelessness. Linné also emphasizes that the mothers' love of their infants increases daily during the nursing period and that mothers love the children they have nursed at their own breast much more than those who have been left to wet-nurses.

Concerning the artificial feeding with cow's milk Linné believes that this form is inferior to the milk of wet-nurses because cow's milk has another constitution and taste since it is derived from a herbivorous animal, and he also believes that the children become silly because the cow is silly. He asks why then dog's milk should not be preferable. The cow's milk is first cooled and then heated and on this acount it is easily modified and becomes further deteriorated by being kept in metal vessels. During his journey in Lapland Linné found that the infant mortality and nativity were excessively great in Västerbotten and he ascribes this to the artificial feeding with cow's milk. The mother in Småland, on the contrary, nurses her own infant and is sorry if she is unable to do so. On this acount she does not give birth to a child every year as do the wives in Västerbotten.

The dissertation terminates with honourable tribute to the nursing mother. "We rightly consider that mother happy who conscientiously does everything that is right and honourable and we predict bodily and spiritual happiness to the infant who suckles its own mother's breast."

In *Lachesis naturalis* Linné devotes a chapter to breastfeeding with practically the same content as the thesis and even slightly extended. Among other things he states that the infants should not be nursed at prefixed times, but only when they crave it, as is the case among animals and among the Morian women, who during the day have their breasts hanging across the shoulders so that the children they carry on their back may feed whenever they want.[1]

[1] Rosén expresses a contrary opinion.

Although Linné in his book about the wet-nurses by and large is a child of his time still he is much in advance of this time. On the basis of his medical authority he dared to challenge the French decadence among the higher classes of society and he did not flatter the circles of the court, as his friend Rosén, who was the physician at the court, was accustomed to do.

Moreover, Linné criticizes the practice of swaddling the infants, not as cautiously as Rosén who first described in details the correct way of swaddling the infant, and then later said that it is wiser never to swaddle the child. Linné writes: "The infant that has been rolled up in the uterus like a squirrel in its nest is stretched out and swaddled and its hands and feet are bound; thus it becomes blue in the face and cries day and night because it is too tightly wrapped." "The Red Indian wraps its infant on a board", he says, "in order that it may later walk straight as a pole, while the Laplander puts it loosely in a wicker basket in order to make it agile and flexible. Still worse is the custom to compress the head of the newborn infants by rollers in order to produce more compactness of the bones and to hasten the closure of the sutures. By this procedure the child may get epilepsy or in all events psychic injury may be produced". He adds, "the greater the brain, the better the intelligence". Another bad habit is to press the ears of the newborn infants against the head, "in order to prevent them from protruding as in farmers". Thus hearing may be impaired.

Linné opposes also rocking the infant that was used in order to silence the crying child. He had seen three types of cradles during his travels in Sweden: 1. those in Småland that are hanging by a rope from the roof and the rocking is made by up and down movements, 2. those in Västerbotten where the rocking movement is made from head to feet, 3. those in Uppland where the infants are rolled from side to side. He writes: "An adult man would become dizzy and get seasick if he was rocked. To toss the newborn child in that way should be regarded as ridiculous. It is not surprising therefore that they get nauseated and vomit as if they were on a rolling ship. Children that are not accustomed to the cradle never cry. The Laplanders' infants remain silent even in the coldest weather without being rocked, they become restless only when they get hungry." Even in this matter Linné has a more decided opinion than Rosén who says that the cradle should be abolished, but later gives a careful description of the best manner to rock, the position of the cradle etc. Remarkably enough Linné seems to change his mind about cradles later, because in 1764 (*Diaeta aetat.*) he writes that they more justly should be regarded as affording an adequate and harmless exercise. Even in our days there prevails a changed attitude toward the use of the cradle which, according to some child-phsychologists, is regarded to promote a soothing effect.

Against rhinitis in infants which spoils the sucking Linné advises to apply majoram-butter and against sweating and soreness of the skin zinc and lycopodium powder is recommended instead of wheat-flour, because the latter is often mixed with mites. The importance of cleanliness is stressed as a prophylactic measure and frequent changes of the clothes, in order to keep the infants dry, are recommended. Linné also emphasizes the infant's susceptibility for convulsions especially in smallpox and during teething and he considers them to depend on their bigger brain and nerves.

During or shortly after the lactation age the sutures are closed, the teeth are developing, the child learns to walk and the babbling is changed to talk (according to Linné this happens in the third year of life, i.e. at about the same age as nowadays). The infants at this age eat chewed food,[1] bread with milk or soup. He warns against meat "because the canine-tooth is not the first one to develop" as he says.

The toddlers laugh and are agile. In order to be lithe and flexible they should learn dancing already at four years of age.

The next age-period is *Pueritia* (playing-age), 7–14 years, from the second dentition to puberty. Linné calls this period our life's budding time, when the play is the most prominent occupation. The right way to play should be taught, "we should not spring as we wish" he says. At this age children are talkative, humorous and ignorant of serious things, they have no patience and they like changes, they prefer to play with children of the same age, the boys ride their hobby-horse and run races. The children should be allowed to roam about in fresh air and to become hardened to cold which improves the general health. He writes: "The sons of noblemen can scarcely stand a gust of wind and become miserable men." The children require food often and much food which should not be denied them. But the food should be easily digestible. "Fruit is the most natural food for children, meat on the contrary is less advantageous." Sweets can be permitted but with some restriction. Because during this time memory is developing and the children remember words and sentences they should start to read but only one hour a day, and they should not have too exhausting studies which demand judgment.[2] They should sleep at least 12 hours at night. Common diseases are pediculosis, scrofula, glands of the neck, and "flowing head".

Adolescentia is the age of young people, 14–21 years, from puberty to

[1] Linné says in one of his lectures that it is an advantage that "wet-nurses chew the food for small infants". In our country chewing food for children still occurred at the end of the 19th century.

[2] Linné talks here as usual about the children of well-off people and mostly about boys, the children of the farmers did not start to read until 15 years of age, if they were taught to read at all (*Laches. naturalis*).

the end of the growth period. The anatomy and the physiology of puberty is correctly described by Linné, rather in detail. Psychologically he characterizes this age-period by such words as sexual thoughts, modesty, changeableness, impertinence, humour, generosity and honesty. During this time seriousness should increase and excessive extravagances should be avoided as well as drinking and sexual intercourse because (he quotes Seneca) "A dissipated youth bequeaths a languishing body to old age" and (he quotes Tacitus about the Germans) "Only during more advanced years do young men fully enjoy a woman's love, and hence they spare their male vigour for those years". In *Lachesis naturalis* he writes about this age-period: "The flower of youth disappears, the flourishing face, the bright eyes.—He who loses the spurs of Venus in young days is without hope. The seed is the oil in the lamp, happy the man who can keep it. The libido is the spur of the genius. Exceptions are Charles XII and the king of Prussia." Apparently Linné insists emphatically on sexual abstinence in youth although it is doubtful if he does so for medical or religious reasons.

The major part of youth is passed in school and this sedentary indoors book-grinding Linné considers to be dangerous: the boys become sad, thin and retarded in their growth. As counterbalance he recommends dancing, playing and sports, such as riding, swimming, fencing, wrestling and outdoor activities such as walking, hunting and fishing. Concerning the dress he warns against too narrow collars for the boys and against corsets for the girls. Sleep should be reduced and teen-age boys should get up earlier than before in order that they should not go through life in sleepy and dull fashion. The meat rations should always be very scanty.

As stated above the rearing of children was a matter dear to the heart of Linné. In *Lachesis naturalis* he writes: "Children's entire education depends on the formation of good habits. God have mercy on those who acquire bad habits, for bad habits are worse than the devil." Aversion for the inculcation of good habits may in later years produce the contrary effect, as for example: "When at first one begins to read, one tires rapidly, but when one gets used to it, one doesn't quit reading without regret." It is surprising that Linné argues against coercion and punishment, which at that time dominated all education. He says: "If one starts out by compelling a boy to read a book and to cane him for not wanting to do so, he may never read another book." In a letter to Bäck he writes about his own 9 year old son: "I observe my son playing the whole day long in the garden without getting tired, but when I force him to do anything, he becomes drenched with sweat and tires within half an hour."

On the other hand children should learn to control their emotions, therefore they should not be permitted to do as they please and become

stubborn. Nor should children be frightened for instance by the presence of evil spirits in dark which may make them clostrophobic for the rest of their life. Linné confides that he himself did not dare to go out alone in darkness before he was 20 years old and adds: "One should beware to deceive a child into believing something, lest it becomes permanently fixed in his mind."

During his various official journeys in the Swedish provinces, as already mentioned, among other things Linné also made observations in children. In his journey in Skåne he tells about a visit to the Foundling Hospital in Malmö: "The hospital housed 126 children of both sexes who were reared in this institution especially adapted to poor children from infancy until they attained 15 to 16 years of age. In one of the schools they were taught to read Swedish, in another Latin and the catechism, in another arithmetic and writing, in still another one to sew, to spin and to make lace". During his visit to Falsterbo he observed that the children were remarkably numerous, which he considered due to the fact that smallpox had not killed off the children because the village was quite isolated.

He reports that he occasionally encountered pediatric cases on his journeys, for which he was called into consultation.

During his journey to Lapland he observed a case of *amblyopia* in a $1\frac{1}{2}$ year old child, probably caused by a congenital atrophy of the optic nerve or a retinochorioidal lesion with a big central scotoma.[1]—In his journey to Öland he tells about a poor woman who asked him about the sex of her child, because a neighbour friend had reproached her that she had the child baptized with a boy's name although it was a girl. Linné writes: "When the child was visited it was found that the penis was totally retracted and did not have an oblong rima but a round opening in which there was a caruncula, large as the end of the small finger. When this was pushed aside the glans penis appeared, but the urine was discharged above the glans. The scrotum with two testicles was situated directly below as in male infants." Apparently it was a case of *epispadia* and Linné recommended that the child should retain his male name.—During the same journey he was consulted about another child. It was a 13 year old boy who was supposed to have been exchanged with another at birth. Linné writes about him in this manner: "He could neither sit, stand nor walk. His hands and legs showed no coordinated movements. He didn't talk but only mumbled incoherently. The canines in his upper jaw protruded and his eyes squinted. It seemed that he was almost deaf. He had thin legs, soft flesh and the facial appearance of a girl rather than a boy. All his movements were so unpleasant that one was afrightened.

[1] The diagnosis is made by Prof. FREDRIK BERG at Upsala and the case has more ophthalmological than pediatric interest and is therefore not quoted here.

He was not a changeling but suffered with a disease called *hieranosos*".[1] This was apparently a case of idiocy which cannot be properly diagnosed on the basis of this brief report.—On his journey in Västergötland Linné encountered many cases of *Spina ventosa*: "The children presented nodules on the legs, hands, arms, in the face and also on the breast. The nodules were big as small apples, some of which were localized in the flesh while most of them were affixed to the underlying bones. They were mostly of hard consistency and painless. Only occasionally did they perforate with production of a little pus. They produced contractures and impaired the underlying bones. This disease occurred in infants and other children up to eleven–fourteen years of age. The children that were once afflicted with this disease remained sick for many years."—During his journey in Skåne Linné described a *monstrum humanum*, i.e. a monster which succumbed shortly after birth: "It was a female infant born without neck and almost without head. The right eye was too large, the left eye too small. The hare-lipped mouth was topped by two big canine teeth. A large fleshy mass hung from the neck. The right arm presented a hairy skin and the left hand had a crooked little finger."—These case reports betray that Linné, like most contemporary scientists, was very interested in "curiosities".

Among children's diseases in which Linné was especially interested may be mentioned *convulsions*, on which subject he has written a special article: "Experiences on Epilepsy in Skåne and Werns" (in the Transactions of the Academy of Science 1742). On his return from the journey in Öland and Gotland Linné visited his native place Stenbrohult, where he was told that local farmers as well as those in the adjoining parishes in Skåne often had treated eczematous eruptions on the head of their children by washing them in cold water, and this treatment brought on epilepsy. Linné states that he had observed that children treated in this manner sustained less "heat in the head", reposed smilingly at their mother's breast and became tranquil and sleepy; the eczema healed although convulsions persisted. It is different in children washed with hot water: their eczema is certainly not removed but they do not sustain any convulsions. In this matter Linné adheres to the opinion prevalent in his time. "Flowing head", that is exsudative diathesis, a term also covering running nose, eyes and ears, was considered a healthy bodily function, by means of which irritating fluids were removed in the same manner as by expectoration, perspiration, urination and defecation. It was harmful to suppress these functions, the unhealthy fluids were then absorbed by the body and attacked interior organs, in this case the brain. The epilepsy in this case was probably either the initial fever

[1] According to *Genera morborum* this disease is characterized by permanent shaking, the body having normal sensitivity.

convulsions or spasmophilia and doubtless occurring after and not on account of the treatment. The prevalence of cold-wet dressings instead of hot ones probably depended on its anti-pruritic effect which hastened the healing. Regarding convulsions occurring in children it may be mentioned that Linné stresses in his lectures, that if convulsions do not disappear at puberty they become permanent, i. e. they mean genuine epilepsy.

Whooping-cough was a very grave disease in Linné's time, and according to statistics not less than 5,832 children died in 1755 in Sweden from this disease (the number of the total population was 1,875,000) and Linné lost his own 3 year-old son in this disease. As mentioned above Linné regarded whooping-cough as due to a living infectious substance, a belief which Rosén and others later shared. No specific therapy was known, but when Linné during his journey in Västergötland was told that people used to treat whooping-cough with an infusion of *Ledum palustre* he tried it; subsequently he wrote a thesis on this subject and had the drug inserted in *Pharmacopoea suecica*, where it was retained until the 7th edition (1879). It is probable that this herb was used because of its narcotic effect which lessened the attacks of coughing.

Linné held that *rickets* was caused by a too intense production of acid in the body which made the bones soft and the muscles and ligaments lax; rachitic infants are therefore best treated by massage, exercise and remedies that prevent development of acid. *Hectica puerilis* (Sydenhamii) or *Febris lenta infantum* (Junkeri) correspond most closely to the *Tabes mesaraica* of later time or tuberculosis of the mesenteric lymphatic glands. It was also called "älta" in Swedish. This disease is characterized by protracted fever, swelling of the abdominal glands, inflamed entrails and consumption of the lungs. According to Linné more children die from this diesase than from any other except for whooping-cough and smallpox (bovine tuberculosis was certainly much prevalent at that time).

Concerning *helminths* Linné knew both spring-worm, belly-worm and tapeworm. At first he had difficulty in classifying them from a zoological point of view and several times he changed their Latin names. First in the tenth edition of *Systema Naturae* (1758–1759) he gave them the names that they have retained until this day. Spring-worm (Oxyuris) he describes in detail and he says: "These worms occur quite frequently in children and one sees big heaps of them leaving the body of sleeping children. They live in the rectum where no medicament can effectively attack them, because it has already spent its force before it reaches the rectum." He believes that the worms live in the soil and are transported by drinking-water, because oxyuriasis occurs more frequently among poor people, "who are not very particular about the kind of water they drink".—Even belly-worm (Ascaris)

he believed came from the soil. "When these worms according to their habit in the soil crawl about and penetrate the finest holes and pores, they produce a severe pain of which children and others infested with them always complain, especially when they attack the more sensitive parts in the stomach, the liver etc." According to Linné the Ascaris worms are driven off by bitter and irritating medicines, for instance infusions of pomerance or green walnut shells.—He differentiated between four types of tapeworms. He knew that the proglottides were individuals of lower rank, but he could not understand the connection because he never saw the head of the tapeworm, and he believed that the sexual openings were suctorial mouths. This group of helminths (it was discussed in a dissertation *De Taenia*) remained for Linné, from zoological point of view, an unsolved problem and he wrote: "A peculiar beast which among all others is the only one oblivious of age, although it may infest man from his youth until he turns old and grey and is buried." Linné considered the tapeworm a symbol of human generations, in which every part is produced by a predecessor, is a separate individual and still is a link in a chain.—Regarding *Trichocephalus dispar* it has been wrongly said that Linné discovered it. Its description appeared first in the 13th edition of *Syst. Nat.*, published by Gmelin 1788, that is 10 years after Linné's death.

It is quite apparent from statements above that Linné was interested in children and their diseases. That he also loved children, both his own and those of others, is evident in his letters. He himself had 7 children and in his letters to Abraham Bäck he discourses affectionately about them. Two of them died, Sara Lena, at 15 days of age in *Aphtis* (probably diphtheria) and his beloved son Johannes, who just had begun to utter a few words, barely 3 years of age in whooping-cough with fever (pneumonia?). When his 3 year old daughter Sara Stina was struck fatally ill by a relapsing fever, he reports in detail to this friend about her illness. "My tiny youngest, loveliest girl, who surpasses all other children of her age in intelligence and attractiveness, now she seems to sleep death's endless repose. I have spent the whole night with her without sleep, so that I might close her eyes, when all signs of death have supervened: irregular pulse, convulsions in the face, choking breathing, plucking on the bed-cover, parched lips and tongue, dull and sunken eyes. At dawn she was still alive and began to breathe a little more freely. I anticipate with awful fear what the oncoming night may bring. I cannot tell you any more, crushed as I am by sorrow over my beloved girl." Later he tells that every fourth hour he administered her quinine and Marum verum (to induce perspiration) for several days, during which time she gradually began to breathe more easily, the sight and hearing returned and she became afebrile. He tells about the delivery of his stillborn

youngest daughter Sophia who was suffocated by pressure of the umbilical cord but after a quarter of an hour's *insufflatoria medicina*[1] she was returned to life and started to breathe.

Linné displayed the same interest for the children of his friend Bäck, especially for the son Carl, who was christened after Linné and in the letters was called "little brother Bäck" or "little Archiater". At 5 years of age this boy received as gift from Linné a collection of shells, apparently with the intention to awaken in him an interest for natural sciences. At 10 years of age this boy visited for one month the house of Linné in Upsala, where he attended Linné's lectures in the Botanical Garden and accompanied him on his botanical excursions and travels to Hammarby. Linné also gave him rare plants for his herbarium. It was with regret that Linné returned the boy to his father: "*Nolens volens* I am constrained to take leave of the little Archiater, although I should love to keep him". Linné was certain that the boy would be a physician, and he followed his development with great interest, gave advise to the father when the boy became ill and wrote: "Don't compel him to read and to exercise before his health is totally restored."[2]

Finally a few lines may be added about Linné's own childhood and what he himself has told about it. His interest in plants he acquired from his father, who in the small parish of Råshult had planted a garden remarkable for its time. Linné tells that his mother often during pregnancy walked in the garden, enjoying its pleasantness and admiring her husband's skillful arrangement of the garden. Linné's father later decorated the infant's cradle with flowers, his toys were made of flowers and when he cried the mother placed a flower in his hand and then he quieted down. When he was 2 years of age the family moved to Stenbrohult, where his father became a vicar. Even here his father planted a garden and later on the boy got his own bed of flowers to plant and to weed, called "Carl's garden". When he was 4 years old he started to learn the name of wild plants. When later he learned to read, his interest was mostly focused on the garden, for which his mother upbraided him, while his father encouraged him.

During the school-years in Växjö the book-grinding of Latin and the catechism were prevailing, especially since the boy was supposed to become a priest, but he had the good fortune to come under the tutelage of a teacher in the gymnasium who understood his special talent and patronized him. This was the lecturer and district physician Joh. Rothman who gave him private instruction in natural history. Linné decided to become a physician rather than a priest.

During vacations at the parsonage Linné collected plants, flowers, insects

[1] Blowing air under pressure into the lungs of the newborn baby, mouth against mouth.

[2] He died already at 16 years of age from consumption, deeply mourned also by Linné.

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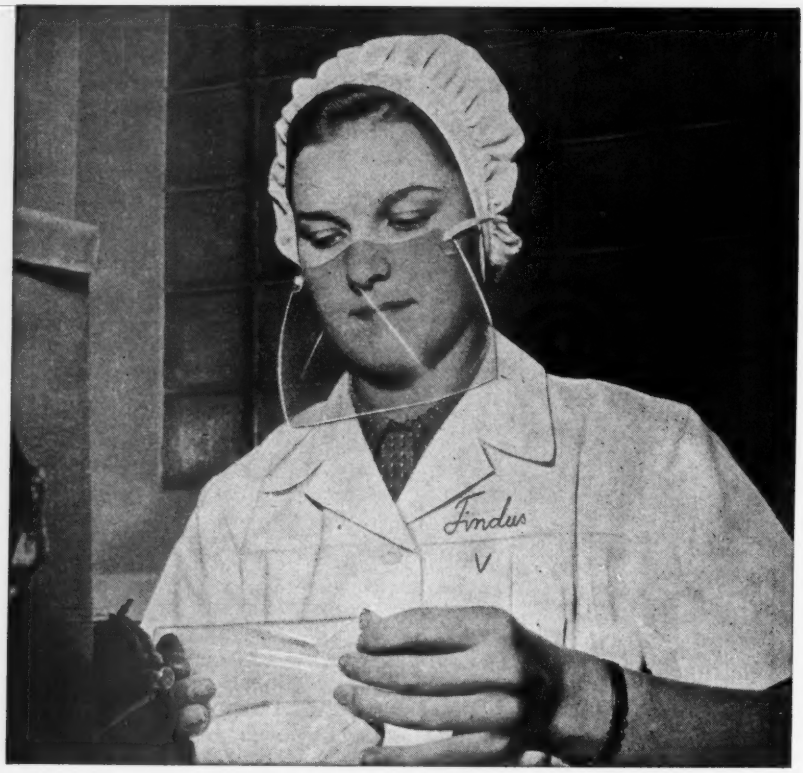

utformning. Början göres med denna annons, i vilken beröres den hygieniska kontrollen av den personal, som arbetar med tillverkningen av Findus barnmat vid fabriken i Bjuv.

En livsmedelsindustri, som tillverkar och distribuerar barnmat, påtar sig ett betydande ansvar. Findus arbetar oavbrutet på att göra sin barnmatstillverkning så fullkomlig som möjligt. Tillverkningskontrollen har drivits så långt som praktiskt är genomförbart. Tillverkningsgången är upplagd i samråd med specialister inom medicinen och bakteriologien.

Den hygieniska kontrollen

All personal, som handskas med livsmedel, måste stå under sträng hygienisk kontroll. Alldeles speciellt måste de hygieniska kraven skärpas, när det gäller framställning av icke helsterila barnmatsprodukter såsom vällingpulver. Findus har ordnat sin hygieniska kontroll på följande sätt.

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All personal, som nyanställes vid Findus, underkastas en grundlig hälsokontroll vid Findus läkarmottagning. Hälsotillståndet hos alla, som sysslar med vällingtillverkning, kontrolleras med jämna mellanrum av bolagets läkare, dr Sven Ranklev. Bakteriologisk odling utföres sålunda varje vecka å hals- och näsprov samt å faecesprov minst 3 gånger årligen. Dessutom utföres Widalprov. Skärmbildsundersökning utföres en gång om året.

Vid misstänkt diarré- eller halssjukdom tages genast kontrollprov och vederbörande får stanna hemma med full lön, tills proven har avlästs. Om smittosam sjukdom konstateras, får vederbörande börja arbeta med barnmat först sedan nya prov visat fullständigt tillfrisknande.

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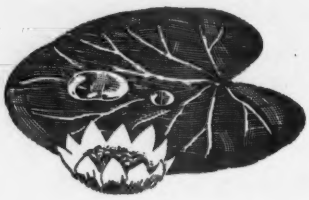
Betydelsen av en hög personlig hygien inskärpes hos personalen genom olika metoder. Företagets läkare håller föredrag i dessa frågor, och en särskild instruktion rörande den personliga hygienen har utarbetats. Brott mot denna instruktion medför förflyttning till annan avdelning eller, i svårare fall, avskedande. Förmännen samt vid vissa tillfällen sjuksköterskan på läkarmottagningen kontrollerar handtvätt och skötsel av naglar.

Arbetet med vällingpulver sker i lokaler, som man söker hålla så sterila som möjligt. Tillträde kan endast erhållas genom särskilda sterilslussar, där ombyte av arbetskläder och skodon sker. Alla, som arbetar med icke förpackat vällingpulver, är försedda med effektiva munskydd.

Dessa fakta är sammanställda av chefen för Findus forskningslaboratorium, docent Carl Erik Danielson.



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PHARMACIA — UPPSALA

and stones and classified them. He amused his small siblings by playing doctor, he felt their pulse, pretended to bleed them and to cure them with drugs made from plants which he knew had medical use.—One summerday he told his father about his decision to study medicine. His father became dismayed, and the young Linné reminded him of his own words in a preceding conversation: "Whatever one is inclined to do, one usually will make a success of", and the father acquiesced for logic's sake, saying: "I will not compel you to do anything for which you have no inclination." His mother consoled herself with the hope that at least her other son Samuel would become a priest. The latter was therefore never allowed access to the garden —and eventually he entered the priesthood.

It was also in Stenbrohult that Linné treated his first child-patient. It happened during the Christmas-holidays that he as medical student had to nurse his own 10 year old sister Emerentia, who was taken severely ill with smallpox. The treatment was grotesque in that she was placed in the disentrailed warm hollow of a freshly-slaughtered sheep in order to inhale its healthy vigour—with the result that the patient was cured.

One can thus say that Linné was hereditarily disposed for his dominant interests and that during his formative years in the home and in school he had the good fortune to live in such a surrounding that his talents could develop freely. He remains a brilliant illustration of the truth in Wordsworth's winged phrase: "The child is the father of the man."

In his more advanced years Linné often quoted the classical words "*Praecocia ingenia raro maturescunt*" (premature geniuses rarely mature) which can also be applied to himself although in another sense than it was intended. During his whole life he had a child's mind, spontaneity, sharp faculty of observation and curiosity about all new things. Although in older years he became gradually pessimistic and considered everything being vain, according to the Ecclesiastes of Salomon and the ancient philosophers, especially Seneca; he had in his old age the faculty of the child to delight in surprises, or in an unexpected act of kindness, as for instance when he received from abroad a collection of plants. "I am delighted from head to foot," he wrote, "at the very sight."

He treasured with pleasure memories of his childhood and native place and in his last days he wrote with trembling and paralyzed hand on a scrap of paper, that was found posthumously "*Nostalgia—Stenbrohult*".

Summary

From Carl von Linné's publications the author quotes and gives an account of Linné's concept and opinion of various matters regarding pediatrics and child health.

Received March 10, 1957

S:t Eriksplan 19, Stockholm, Sweden.

Acta Pædiatrica 46: 232—237. May 1957

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Dwarfism in Siblings

Two Case Histories With Comments By Carl von Linné

by ARVID WALLGREN

In Transactions of the Swedish Academy of Science for 1745 the member of the Academy, Samuel Sandels, Councellor to the Mining Department of the Dalecarlian County, presented a brief description of two siblings with dwarfism. The discussion of the probable causes of the small stature of these two children was conducted by Linné, who attached some interest to them because they displayed some peculiar habits, customary in Sweden at that time. The Swedish entomologist and Linné-expert, Dr. phil. Felix Bryk, kindly called my attention to this intervention of Linné, that seemed to have been overlooked previously.

The report of these two cases to the Academy of Science was suggested by Linné (Carolus Linnæus). When Linné in 1745 made a scientific excursion to Dalecarlia he visited the city Hedemora, where he saw the two dwarfs. Sandels' report runs as follows:

"On August 9th, 1745, Professor Linnæus passed through Hedemora and happened to see in my house two siblings, a boy and a girl, who because of poor and unsatisfactory breeding had remained so small in stature that one seldom finds their equals. The girl, aged 9, one would believe to be only 4. The boy, aged 7, was so small that one would consider this an exaggeration and that his true age was instead 2 years. The case of the boy deserves special consideration and Professor Linnæus advised me to send a report of him to the Royal Academy of Science to which request I tried to comply immediately."

"The boy was examined in the presence of Professor Linnæus, the Lord Mayor Hollsten, the Vice-Parson Gangner and the Vice-Judge Dahl and the findings were as follows: The boy Johan Ersson was born November 26th, 1738, according to the registry book of the church of Hedemora. His father was boatswain Erik Berg and his mother Sara Johansdotter, neither of them small nor thin but of ordinary stature. This 7-year old boy

To the 250 anniversary jubilee of the birth of CARL VON LINNÉ.

was measured with the steel yard of by the Councellor of Commerce Polhem and the boy's body weight was found to be only one lispound and three marks (about 9.8 kg), his total height, measured with the same steel yard, was found to be one and a half yards and one inch (about 69 cm)."

"In order to show the marked difference between this child and children in general another boy, who was 7 years of age, was measured and his body weight was two lispounds and four marks (about 18.7 kg), and another child whose body weight corresponded to that of the dwarfed boy, namely one lispound and three marks, had not yet attained $1\frac{1}{2}$ years of age."

"The undersized stature of the boy could not be due to any hydropsic cause; the protrusion of the abdomen as compared with the height was due to the great amount of food he consumed whenever he ate. The size of the head corresponded to the body size and his underdevelopment could therefore not be due to hydrocephalus. His joints were not abnormally large and hence he could not be rachitic. Neither was his back abnormal which, when kyphosis exists, may retard the growth of the body."

"The true cause of the pronounced smallness of the boy must be due to malnutrition. His mother, a poor widow, had not enough food to feed the children and in addition considered alcohol a superior nourishment to any other kind of food; from motherly love she provided her children with this nourishment which thus retarded their growth. It is known that people who breed puppies to pet dogs use every ruse to force them to drink alcohol in order to produce permanent dwarfs in their species. One finds that this boy's fat is soft and smooth and is not at all dry. The face is neither markedly yellow nor dark although the color is perhaps somewhat darker probably due to sun-tan."

"The case of this unfortunate boy shows how irresponsible it is of poor people in many places, not least in Stockholm, to feed their children bread dipped in alcohol in order rapidly to induce them to sleep without crying, or to put a glass of alcohol in front of the child and let him dip the bread himself in order to console and quiet him while the parents are away at work. It is easy to understand how such a bad habit makes the children small, delicate and thin, and produces bad health in the adult population. Here I may remind of the different effect alcohol has from that of beer. One observes in the iron mining districts that the miners who drink their good and well-brewed beer become large, fat and healthy looking. I know a miner, C.D., whose body weight for this reason was twentyseven lispounds (about 229 kg (!) without having dropsy."

"Professor Linnæus told me that he had seen in the market place in Amsterdam a child that was exhibited for money and whose mother called him the "Small Cajanus" because she believed that Cajanus, which name

in Sweden generally connotes "the tall Finn", was the father of her child, although Cajanus perhaps had never seen the mother. This boy aged 3, was so fat that he could not stand without having his legs placed widely apart. The mother weighed him in the presence of spectators to prove that his body weight was exactly seven lispounds, Dutch scale. This unusual adiposity had developed from consumption of sweet beer and the mother who had neither had breastmilk nor cow's milk to feed him, had accustomed him to drink beer and she kept the jug always near him to drink from and this he did continually and not fraudulently."

From the data given it is not possible to state anything definite about the true cause of the dwarfism in these two children. That undernutrition can produce poor bodily development is an every-day experience in Far Eastern countries with their prevalent or exclusively rice or corn diet, which contains insufficient amounts of essential aminoacids. Such kwashiorkor children of 2–4 years of age look as if they were only 6 months old. They suffer concurrently from other evident deficiency diseases, especially avitaminotic states of different kinds and degrees and in particular from xerophtalmia and pellagra. Deficiency diseases of such a degree often have a poor prognosis and the children look very ill. The reported case of dwarfism was apparently free from any marked sign of avitaminosis, if one is allowed to draw any conclusions from the record. The boy seems to have been in a rather satisfactory state of health. The pigmented skin may, however, indicate a niacinamid deficiency. The dwarfism may be partly due to deficient nutrition, but the marked underdevelopment of the body combined with the absence of evident signs of avitaminosis makes it, however, more probable that some hormonal or genetic disorder played an important role in the development of the dwarfism. In the Chicago Pediatric Society, Dec. 16th 1952, Steiner reported on a pair of siblings with pronounced dwarfism depending upon complex hormonal disturbances. The oldest of these children, a 10 year old boy, was only 50.8 cm in height.

I will not go into further discussion of the probable causes of the underdevelopment in the reported cases as this would only be guesswork with the scant information of clinical data available. Of greater interest from a pediatric point of view is the pretended cause of the dwarfism: the great alcohol content of the supplied nourishment as suggested by Linné and the popular opinion of the value of beer as an adequate food even for children.

As professor of medicine at the University of Uppsala Linné presents in his teaching a surprisingly great amount of common sense and sound wisdom of life. In his teaching of medical matters he also gave lectures on "dietetics", which in his vocabulary means "individual health", a subject that interested the physicians very much at that time. These lectures have been published

and constitute an encyclopedia on contemporary medical health methods. In these lectures he discusses different kinds of popular Swedish dishes, their advantages and their disadvantages. Some of these lectures were used for the popular education of people. For that reason they were printed in the booklet that was most extensively sold and cheapest in the past in Sweden, namely the Almanach.

In 1747 the Almanach contained information about coffee, in 1748 about alchohol, in 1749 about beer. In the latter article Linné first gives a detailed description of how to prepare good beer, how important it is that its different constituents are of excellent quality, and that it is brewed with experience and scientific skill. Then he explains why some kinds of beer may produce disorders in the human body and why an excellent beer was by him regarded as the best possible drink for the Swedes, especially for those who exercised a great deal or had hard work to do. Such a good beer "does not heat the blood" as does wine and is very nutritious as is seen in heavy beer drinkers, who although they do not eat much food, are still fat. In this connection he also refers to the fat boy seen in Amsterdam and mentioned above. He warns those of the upper class to use beer because they have too little exercise and he also warns against drinking beer on hot summerdays. He is of the opinion that in certain parts of Sweden a better beer is brewed than anywhere else in Europe and he recommends that every university student should be taught the production of good beer and to propagate this knowledge in their home counties.

Linné's pamphlet "Comments on Alcohol", first printed in the Almanach in 1748, has later been reprinted 12 times, the last as a facsimile edition by Felix Bryk. At the same time as Linné recommends a good beer as something valuable for the health, he warns that the use of alcohol "coagulates or clots all fluids in the human body, except the urine and makes all fibres or strings in the body stiff and brittle". He gives a vivid description of the dangers of the excessive use of alcohol but admits that, when it is used prudently it may produce what no other drink can do, namely the enlighting of life and spirits. He reports from his own experience that alcohol is used in hospitals and in the army as prophylaxis against diarrhoea and bleeding (blod clot), but "unfortunate the man who has no other antidote and treatment for contagious diseases". He warns the farmers against the custom of giving alcohol instead of other food for breakfast to their helps and against the popular opinion that alcohol can be given as a sole nourishment in order to spare other kinds of food during the whole day. "But never has anybody become as fat from strong drinks as from such soft drinks as for instance beer, milk etc."

He writes: "May God forbid that anybody should give alcohol to children who are still growing, because the finest strings of life, which are being lengthened at that time, thereby are made brittle and hard and thus may break too easily. If one gives alcohol to puppies or rub their backs with

alcohol they are transformed from the largest kind of dogs into small poodles."[1]

He mentions that in Utrecht there was a young man aged 20 years who supervised the arrival and the departure of the ships and who due to too much use of alcohol was not taller than an 8 year old boy. "Thus it is unwise of people in Stockholm and elsewhere to refresh delicate children with bread soaked in brandy. One should not be mislead by the observation that alcohol drinkers are corpulent since it is a natural advantage to surround by fat those parts of the body which are exposed to excessive stress as for example the kidneys and intestines."

In the 1756 dissertation "Fundamenta valetudinis" Linné returns in some sentences to the question of the effect of alcohol on the growing child[2]. "To suckle its own mother is to drink from the same source that gave life and growth in the mother's vomb."—"If the wet nurse often consumes alcohol then the suckling infant will emaciate or even risk its life."—"Brandy makes children small and thin."

He stresses the importance of preventing people from being weakened from youth on by the unfortunate custom of sipping alcohol which makes them die early from the three prevalent diseases which Linné considered were produced by alcohol, namely: "fever, jaundice and dropsy". He puts the issue on a national economic plan by maintaining that in some small towns in Sweden more than 100,000 barrels of grains were used for making brandy and only 25,000 for food, while the country had not succeeded to produce the grains necessary to feed the population but must import many thousands of barrels of grain annually, which in turn produces an economic deficit for the country. This situation could be prevented by using the grain raised in the country for human food instead of for the production of alcohol.

In the thesis by FREDRIK LINDBERG sponsored by Linné, November 7 1752: "The Wetnurse as Stepmother", translated from Latin by OLOF THULIN and commented by TELEMAK FREDBÄRJ, the author quotes Deodatus about a girl, 7 years of age, who already at this young age was fond of strong drinks because she had had a wetnurse who was a drunkard. Linné quotes also other ancient authors who claimed that the emperor Nero had a wetnurse who was addicted to alcohol and caused a hankering for drinking in her nursing. Women working on farms often imbibe alcoholic

[1] I have discussed the matter of the influence of alcohol on animals with several professors at the Veterinary Medical School of Stockholm and have studied available literature on the subject without getting any support for this concept of Linné regarding such an effect of alcohol on puppies.

[2] Drake of Hagelsrum, G., Linnés disputationer, page 155. Nässjö 1939.

drinks when they are fatigued from heavy field work, and they tolerate strong drinks very well as long as they are engaged in heavy work. When they serve as wetnurses they lead a lucrative life which changes this situation. It has happened more than once that, after their breasts have been suckled dry during the night, they too eagerly have taken to alcohol in order rapidly to satisfy their hunger. This brings about that the infant becomes convulsive and eventually dies as soon as he touches the breast. Linné writes in his "Dietetics" that when the wetnurse gets up early in the morning to give breast to the infant she drinks a lot of alcohol without consuming other food. If she nurses the infant a quarter of an hour later it will get convulsions and die. Moreover if the wetnurse drinks much wine her milk will produce a rash in the infant.

"That alcohol coagulates breast milk is proved by observation in wetnurses who are addicted to alcohol and who suffer with breast abscesses."

In 1764 another thesis was published: "Spiritus frumenti" which had largely the same content as the Almanach article 1748, reprinted lastly 1922 (Klemmings). "A person that is exhausted from work, travel or other exertion is immediately restored by a drink while it takes some hours for food to produce the same effect. Those who travel through the Arabian and Persian sand deserts in excessively hot weather feel more refreshed by a glass of good brandy than from other drinks or food; from this it follows that brandy later brings more coolness than heat."—"Those who at present travel in our country may at every step refresh themselves with a glass of brandy without experiencing dizziness or other troubles although ordinarily they cannot support a mouthful of it. I myself am unaccustomed to this drink", says Linné, "and I am astonished that labourers can take it several times a day without experiencing any evil effects and they even feel refreshed by it. Labourers in our mines or ironworks prefer it inasmuch as they otherwise cannot tolerate the sweating brought on by the heat and the subsequent exhaustion. One observes daily during the summer that sweating is prevented by alcohol."

Summary

Comments on a case report on dwarfism in siblings from 1745 sponsored by Carl von Linné and by him regarded as due to alcoholism in the children.

Acta Pædiatrica **46**: 238—248. May 1957

From the Department of Health of the Netherlands Institute of Preventive Medicine, Leyden

Adolescent Mortality in The Netherlands. II[1]

by J. BRAAKSMA-DE LINT and J. H. DE HAAS

7. The Influence of the First and Second World Wars

As mentioned in the first part of this study, among adolescents, too, the years of the First and Second World Wars were characterized by a higher mortality. In 1918 rates rose to 68 per 10,000, which is more than 2½ times as high as in 1914 (Fig. 5). Not until 1921 was the prewar level reached again. The sharp rise in mortality rates at the end of the First World War was mainly due to the notorious epidemic of "Spanish Flu". In 1918 mortality rates from influenza and respiratory diseases among adolescents were nearly 300 per 100,000, in the years preceding and following the epidemic they were about 13 per 100,000, although it seems that in 1919 and 1920 mortality from influenza (pneumonia) was still relatively high.

As early as 1915 tuberculosis mortality was beginning to increase, 1914 figures being reached again in 1921. During the four years of war tuberculosis mortality rose from 136 to 225 per 100,000. This leads to the conclusion that during the First World War, even though this country was not involved, non-specific resistance diminished fairly quickly as food supplies became deficient and the food situation deteriorated accordingly (Sa̲et).

Death from various other causes showed a smaller increase.

The pattern of death during the Second World War is completely different: the relative increase of total adolescent mortality was greater than during the First World War, viz. from 13 to 45 per 10,000. This increase was largely caused by death from accidents, which rose from 20 to 160 per 100,000 in 1945, three fourths of which being the immediate result of acts of war or accidents with fire-arms.

Deaths from unknown and unreported causes rose from 3 before the war to 100 per 100,000 in 1945.

Mortality from infectious diseases rose from 5 to 53 in 1945. The greater part of this rise was due to an increase in diphtheria mortality (van den Berg & de Haas, 1956).

[1] Part I has been published in the January issue of Acta Pædiatrica.

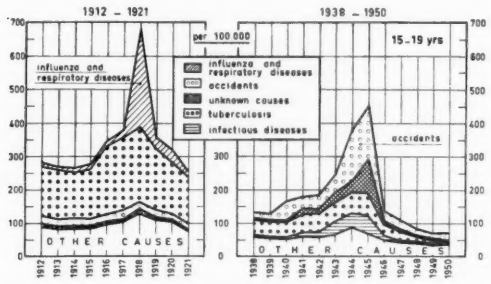


Fig. 5. Increasing mortality in adolescence by cause during the First and Second World Wars.

Besides direct consequences of the war, as air raids and the like, malnutrition was probably the main "cause" of increased mortality, which especially reflected itself in the lists of tuberculosis, infectious diseases and unknown causes. A comparison of the two sections of Fig. 5 makes it clear that in both world wars tuberculosis mortality among adolescents increased by about 50 per cent, but that this increase had a far greater significance during the First World War. While during 1914–1918 this country was not directly involved in the war, tuberculosis among adolescents had wider scope than in 1940/1945. Reversely, the significance of accidents was, naturally, far greater during the Second World War (in which this country *was* involved).

A comparison between mortality during the Second World War among school children (van den Berg & de Haas, 1955) and among adolescents (Fig. 5) shows a certain resemblance. Infectious diseases among school children were a greater relative cause of increased mortality than those among adolescents. Both age groups did not show a marked increase in tuberculosis mortality.

In 1946 tuberculosis mortality among adolescents was clearly below prewar level, mortality from other causes and total mortality following suit one or more years later.

In retrospect it does not seem a mere coincidence that tuberculosis went ahead.

After both world wars it took only 2 to 3 years for mortality rates to reach the figures again which were to be expected on grounds of prewar trends. Among adolescents, too, the decrease in both total and tuberculosis mortality took place far more rapidly than the increase. This stresses once more the great importance of *general* resistance, which rapidly improved after the wars. The increase in tuberculosis mortality was not equally great everywhere. In Amsterdam, almost twice as many adolescents died from

tuberculosis in 1945 as in the years 1935/39, in spite of the fact that inhabitants of the city dying elsewhere were not included (Neurdenburg). Over the whole country tuberculosis mortality in 1945 was 1½ times as great as during 1935/39. Among all age groups in Amsterdam during the war tuberculosis was found to have been a greater relative cause of death than it was over the country as a whole. This unfavourable situation in the big city supports the view that the diminishing of *non*-specific resistance (food shortage) has been the predominant factor.

The increase in tuberculosis mortality during the First World War shows trends with similar peaks for adolescents and school children. During the Second World War the curve of adolescent tuberculosis mortality more resembles that of adults (with a peak) than that of children (with a level top). This is an indication that non-specific resistance among adolescents had decreased more than that among school children, which may be connected with the extremely high need of food in adolescence and, correspondingly, the greater relative lack of it during war time.

8. Regional Differences

Since the beginning of the century adolescent mortality by provinces has presented an irregular picture, none of the provinces showing a continuous maximum or minimum during this period. Adolescent mortality also varies with the size of the municipalities: since the beginning of the twentieth century adolescent mortality in towns of more than 100,000 inhabitants has been below the national average.

During the last few years adolescent mortality in the big cities has been nearly 20 per cent lower than in the smaller communities. Only part of this

TABLE 6

Mortality of adolescents by size of municipalities per 10,000.

Size of municipality	1895/1904	1905/1914	1952 + 1954[a]
< 5,000	35.8	30.3	5.7
5,000–20,000			5.7
20,000–100,000	37.9	28.6	
> 100,000	33.4	28.1	4.7
Netherlands	37.3	29.5	5.4

[a] 1953 excluded because the floods in the South West of The Netherlands affected unfavourably mortality rates in small communities.

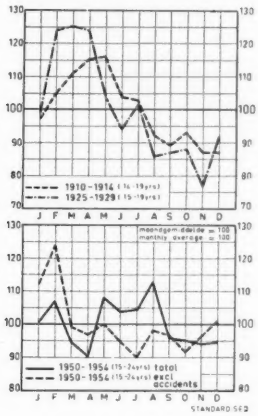


Fig. 6. Monthly deaths among adolescents 1910–1914, 1925–1929, 1950–1954.

difference can be attributed to higher mortality from accidents and tuberculosis in small municipalities. Mortality from practically all causes is higher in rural than in urban districts.

The low figures for adolescent mortality in densely populated Western Holland (with 40 per cent of the total population) are connected with the fact that in these provinces about half of the 15–19 age group live in the big towns.

9. Seasonal Differences

In the beginning of the twentieth century annual adolescent mortality shows ups and downs at specified periods of the year: in spring and early summer it was considerably higher than in full summer and in autumn (Fig. 6).

During 1950/1954 the seasonal pattern appears to be different, total mortality was highest in summer, although there was also a slight rise in winter. Around 1930 this change was beginning to manifest itself. It was possible to study monthly mortality figures for the age group 15–24 over the period 1950/1954 with respect to causes. Excluding accidents the pattern of mortality averaged over each year was practically the same as that of the beginning of the century. This means that at present the seasonal character of total adolescent mortality is determined by accidental death and that this was probably already the case after 1930. The same change has taken place with regard to school children and for them, too, the mortality pattern, excluding accidents, is the same as it was at the beginning of the century.

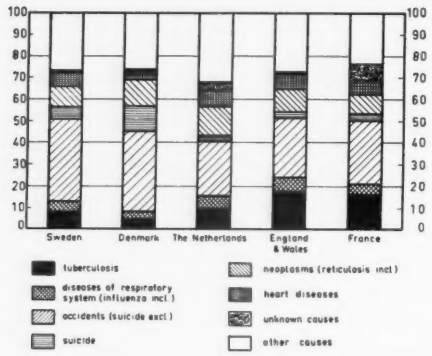


Fig. 7. Leading causes of death among adolescents in some European countries 1950–1952.

10. Adolescent Mortality Abroad

The favourable development in mortality figures in general during the last few decades in nearly all neighbouring countries has also resulted in a marked decrease in mortality among the 15–19 age group (Delaporte, Lindhardt, Logan, Stocks).

As shown by Table 7 of five Western European countries The Netherlands had lowest adolescent mortality figures, although differing little from Denmark and England and Wales. Consequently, in 1953, when The Netherlands were struck by the floods, mortality in Denmark and England and Wales was lower.

As child mortality decreased, excess mortality among boys arose, or made further progress. In general, the ratio boy mortality/girl mortality increases according as (general) mortality is lower. Excess boy mortality is largely due to higher accidental death among boys: in Denmark in 1952, it was more than twice as high as among girls, in The Netherlands and France nearly four times, in England and Wales more than five times and in Sweden nearly nine times.

A pattern of causes of death has been drawn up for these European countries (Fig. 7).

Some difficulty arises from the fact that reports are termed in varying classifications: Sweden and France use the international list of causes of death of 1948, intermediate list, and The Netherlands, Denmark, England and Wales the detailed international list of causes of death of 1948. The groups of causes of death have been co-ordinated as much as possible.

Besides differences in classification, other factors play a role, especially diagnostic differences, which make a mutual comparison of patterns of

TABLE 7

Total mortality, mortality from tuberculosis and mortality from accidents among adolescents in some Western European countries 1946–1952.

Country	Boys				Girls				Total			
	1946	1949	1952	1954	1946	1949	1952	1954	1946	1949	1952	1954
(a) Total mortality per 10,000												
The Netherlands	16.9	8.4	6.8	6.5	10.1	5.3	4.2	3.9	13.6	6.9	5.5	5.2
France	18.6	13.5	10.8	—	15.8	10.2	6.5	—	17.2	11.9	8.7	—
England & Wales	15.3	12.7	9.0	7.7	13.0	9.6	5.1	4.6	14.1	11.0	6.3	6.1
Denmark	13.2	8.7	8.6	8.8	11.7	6.6	5.7	3.7	12.1	7.7	7.2	6.3
Sweden	14.6	11.0	10.6	—	11.0	5.3	4.6	—	12.8	8.2	7.7	—
(b) Mortality from tuberculosis per 100,000												
The Netherlands	32.7	10.1	1.9	0.7	36.2	11.8	3.1	1.0	33.9	10.9	2.5	0.9
France	43.9	20.3	8.3	—	60.8	31.9	11.2	—	52.3	26.1	9.7	—
England & Wales	40.8	21.6	6.2	2.4	58.1	41.9	8.8	4.6	50.9	32.8	7.5	3.5
Denmark	17.2	4.1	1.3	—	33.1	9.8	1.4	0.7	24.3	6.9	1.3	0.3
Sweden	34.2	14.5	5.6	—	52.7	11.0	6.3	—	43.3	12.8	5.9	—
(c) Mortality from accidents per 100,000												
The Netherlands	50.3	27.4	22.7	31.6	8.5	6.8	5.9	8.9	29.8	17.3	14.5	20.4
France	50.6	48.7	50.3	—	12.6	12.1	13.7	—	31.7	30.6	32.2	—
England & Wales	42.2	41.4	41.5	34.8	12.2	8.2	7.7	8.1	23.4	23.1	24.2	21.6
Denmark	53.6	52.8	42.4	58.0	27.0	18.2	19.9	16.5	39.2	35.8	31.4	37.5
Sweden	52.0	51.8	60.7	—	16.0	8.1	6.8	—	34.3	30.2	34.1	—
(d) Mortality from suicide per 100,000												
The Netherlands	2.7	2.9	2.0	2.4	0.8	0.5	0.5	0.5	1.7	1.7	1.3	1.5
France	3.4	3.6	4.9	—	2.2	1.7	2.1	—	2.8	2.7	3.5	—
England & Wales	3.0	3.3	3.4	2.5	1.5	1.5	1.1	1.2	2.2	2.3	2.2	1.8
Denmark	9.3	9.5	6.6	8.4	18.9	6.3	6.9	4.6	13.6	7.9	6.7	6.5
Sweden	6.7	4.7	4.7	—	1.8	1.9	1.0	—	4.3	3.3	2.9	—

causes of death in different countries a difficult task. This is also the case when districts within the same country or different periods are compared.

The significance of tuberculosis varies widely: in England and Wales for the period 1950/1952, tuberculosis mortality was about 17 per cent of the total mortality, in France 16 per cent, in Denmark, however, 4 per cent, and in The Netherlands and Sweden 9 and 8 per cent respectively. The significance of death from accidents also varies considerably: from 27 per cent in The Netherlands to 48 per cent in Denmark. In Denmark suicide as a cause of death among adolescents is of great importance: 10 per cent of the total mortality is caused by suicide, i.e. nearly seven per 100,000. In

The Netherlands only 3 per cent of the total adolescent mortality is caused by suicide, i.e. nearly two per 100,000. In various countries death from suicide is considerably higher among boys than among girls. In Denmark, with a relatively high suicide rate amongst adolescents, the excess boy suicide mortality is not constant.

Death without known or stated cause varies from 8.2 per cent of the total mortality in France to 0.8 per cent in Sweden.

A pattern of causes of death is like a snapshot. Adolescent mortality in The Netherlands has shown a sharp decrease after 1946, which was largely due to the decrease in tuberculosis mortality among adolescents (Fig. 2). Around 1947 the situation was reached which would presumably have applied but for the intervention of war and occupation. After 1947, however, the decrease in mortality figures did not continue at the same slow rate as before the war, but at an increased speed. This phenomenon is not restricted to The Netherlands, but it can also be observed in neighbouring countries. Of these five countries The Netherlands show the lowest figure for adolescent mortality, but the differences are becoming smaller and smaller and tend to lose their significance.

11. Future Trends

Is the conspicuous decrease in adolescent mortality in The Netherlands likely to continue, or has, in Geary's terms, the "absolute lower limit" been reached?

As was shown in the preceding chapters, there exist marked differences in adolescent mortality in certain districts and under specified circumstances. *It seems possible by analysing the minima to predict future rates attainable at an accumulation of favourable factors.*

Adolescent mortality rates in The Netherlands are for more than 60 per cent determined by the four major causes of death: violence, neoplasms, tuberculosis and infectious and respiratory diseases.

As shown in Table 7, adolescent mortality in Western Europe is lowest in The Netherlands. In the five countries considered there is a striking resemblance between the respective rates of mortality from neoplasms, infectious diseases and diseases of the respiratory system. The high accident mortality in Denmark is largely caused by the high mortality from suicide (7 per 100,000). In Sweden accidental death is especially very high among boys (Table 7).

The low rates of tuberculosis mortality existing in Denmark were reached in The Netherlands some years later.

Total adolescent mortality in The Netherlands is now down to 50–55 and tuberculosis mortality of adolescents to $^1/_2$–1 per 100,000.

Mortality does not only vary in relation to country but also within one country the level and pattern of adolescent mortality show regional differences. Mortality figures for the provinces of Noord- and Zuid-Holland for the years 1950/52, which were then 15 per cent below the national average, were reached for the country as a whole in 1954. Mortality in municipalities exceeding 100,000 inhabitants was only 4.8 per 10,000 in 1950/52. It is likely that before long this figure will apply for the whole country.

Adolescent mortality figures also differ in relation to sex: girl mortality between the ages of 15 and 19 years is two-thirds of that among boys. In view of the development up to the present day it is likely that in future total adolescent mortality may decrease to the rates already existing for girls in the big towns: 3.5 per 10,000. If the seasonal variations found for the whole country also exist in the big towns, girl mortality there will reach a minimum of 3.0 per 10,000 during the favourable months of the year.

If this low mortality figure should become the national average, the lives of about 200 adolescents will be spared annually. Medical care for adolescents, so urgently wanted, will hardly need to aim at fighting death, but can concentrate upon the promotion of health.

Will this be the first time in the history of medicine that a new branch is added to the organization of medical care not in order to fight death, but solely to promote health?

Summary

(*The figures correspond to the 11 sections of the paper*)

1. The number of adolescents increased since 1900 from about 500,000 to well over 800,000: their percentage of the total population decreased from 10 to 7.5 per cent.

2. During the last fifty years adolescent mortality decreased to one seventh, in 1955 it amounts to 5.4 per 10,000 (for boys and girls 6.2 and 3.6 respectively). This decrease has been almost as rapid as the decline in infant and school child mortality. Pre-school child mortality decreased even more, viz. to one tenth. After the Second World War the decrease in adolescent mortality has accelerated.

3. In the 15–19 age group mortality among girls has decreased most. At the beginning of the 20th century there existed a slight excess mortality among girls, mainly caused by a higher tuberculosis rate. Since 1930 there has been an excess male mortality amounting to more than 75 per cent mainly caused by accidents. Apart from tuberculosis mortality there has always existed an excess mortality among boys.

4. Up to 1920 tuberculosis caused about 50 per cent of the total mortality of the 15–19 age group. For girls this percentage even amounted to 60 per cent. In 1950/52 only 9 per cent of total mortality was caused by tuberculosis. In 1953/54 accidents are the leading cause of death in adolescence (38 per cent of the total mortality), neoplasms rank second (18 per cent) and tuberculosis comes in the fifth place (3 per cent).

5. Tuberculosis mortality among adolescents decreased from 186 per 100,000 (about 1900) to merely 0.6 in 1955. This spectacular decrease was even more rapid for girls than for boys. The excess mortality among girls from tuberculosis, however, still exists.

Both world wars have had an unfavourable, though temporary, influence on tuberculosis mortality among adolescents; the trend has remained the same.

6. Mortality from accidents has hardly decreased. The relative importance of death from accidents, therefore, has increased since 1900 and accidents now form the leading cause of death also for this age-group. Mortality from accidents among boys is three to four times as high as among girls. Nowadays traffic accidents are the greatest single cause of accident mortality (40–50 per cent). About 1920 drowning was the leading cause of accident mortality. The significance of drowning has decreased absolutely as well as relatively.

7. During both world wars adolescent mortality increased. The increase during the First World War was partly caused by an increased tuberculosis mortality, but mainly by the epidemic of "Spanish flu" in 1918/1919.

During the Second World War the increase was caused mainly by a greater number of deaths from accidents. Mortality from accidents increased to 160 per 100,000 in 1945. The greater part of this increase in mortality from accidents was directly caused by the war.

In 1944/1945 there was a sharp increase in the number of deaths from unknown causes (from 3 to 100 per 100,000). Deaths from tuberculosis increased as well, though not to the same degree as in 1914/1918.

8. There are regional differences in adolescent mortality. In 1950/1954 mortality of the 15–19 age group was lowest in Western Holland. Adolescent mortality in towns with more than 100,000 inhabitants is lower than in smaller communities. This difference is only in part accounted for by a lower tuberculosis and accident mortality.

9. Seasonal influences in adolescent mortality are manifest. During the last few decades there has been a peak during summer, caused mainly by the higher number of accidents.

Excluding accidents, there is a higher mortality in spring more or less corresponding to the total adolescent mortality figures of around 1900.

10. Sweden, Denmark, France, and England and Wales show about the same development as The Netherlands, though on another level. Total adolescent mortality has rapidly decreased, tuberculosis mortality has decreased even more quickly, accident mortality has decreased little if at all, and excess male mortality has increased significantly. Compared with these countries The Netherlands are in a favourable position as regards both total mortality and mortality from specific causes. Only Denmark has a lower tuberculosis mortality.

11. At a continued cumulation of favourable factors a decrease of adolescent mortality to three per ten thousand seems possible before long.

Mortalité des adolescents aux Pays-Bas.

Cette analyse est une des premières études détaillées sur la mortalité des adolescents. Aux Pays-Bas, le niveau de la mortalité des adolescents a baissé à un septième pendant ces derniers 50 ans. Il a atteint 5,4 pour dix milles (7,2 pour les garçons et 3,6 pour les filles). La mortalité des filles a diminué plus rapidement que celle des garçons. Il y a eu depuis 1930 un excès de mortalité masculine parmi les adolescents, dû principalement aux accidents. En 1920 la tuberculose causait encore 50 % de la mortalité parmi les adolescents. En 1953/1954 ce pourcentage est de trois. L'importance relative de la mortalité par suite d'accidents s'est accrue à un tel point, que les accidents sont devenus la principale cause de décès aussi pour ce groupe d'âge. Ceux de la circulation jouent le plus grand rôle. Des influences saissonières sont plus manifestes que les différences

PFIZER, upptäckaren av tetracyklinet, fortsätter som banbrytare inom utvecklingen av livsräddande antibiotika.
En ny antimikrobiell substans, oleandomycin har upptäckts, vilken i kombination med tetracyklin löser resistensproblemet i samband med behandling med bredspektrum-antibiotika.
Namnet på denna kombination är

Sigmamycin

oleandomycin-tetracyklin

Sigmamycin är verksamt mot många stafylokockstammar och andra bakterier, som förvärvat resistens mot övriga bredspektrum-antibiotika. Sigmamycin fördröjer utvecklingen av nya resistenta stammar. Sigmamycin har genom kombinationen oleandomycin/tetracyklin en utpräglat synergistisk verkan.

Pfizer

Sigmamycin

Den nya kombinationen tetracyklin-oleandomycin har större antimikrobiellt spektrum än tidigare kända antibiotika, vilket även inkluderar »resistenta» stafylokocker och förhindrar uppträdandet av nya resistenta bakteriestammar

synergistisk effekt

Den synergistiska effekten påvisad in vitro mot antibiotika-resistenta stafylokocker*

tetracyklin

oleandomycin

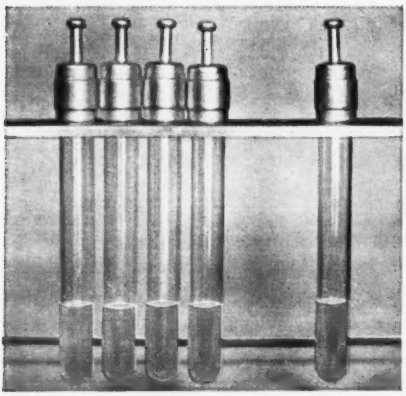
ett nytt Pfizer-antibiotikum

Sigmamycin

synergistiskt verkande kombination av tetracyklin och oleandomycin

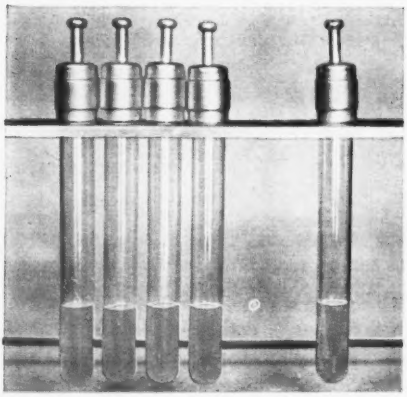
* *Successivt minskade mängder av antibiotikum har satts till en serie rör innehållande konstant mängd buljong. Varje rör ympas med en konstant mängd av den standardkultur, som prövas, i detta fall stafylokocker. Den minsta mängden antibiotikum, som hämmar växten och således ger en klar, ej av bakterier grumlad buljong, anger bakteriens känslighet för antibiotikum.*

Antibiotika-resistenta bakteriekulturer av M. pyogenes var. aureus No. 1433

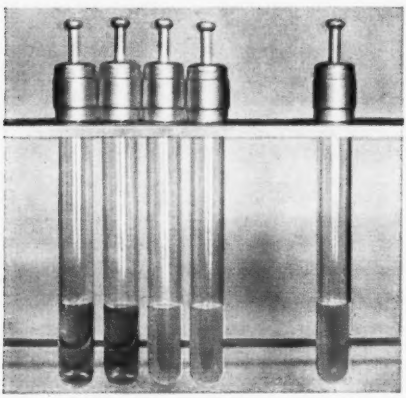


Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
tetracyklin: ingen hämning av bakterieväxten

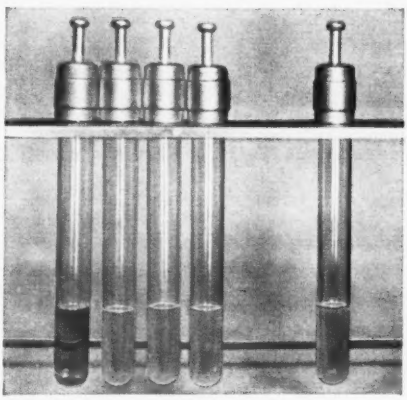
Antibiotika-resistenta bakteriekulturer av M. pyogenes var. aureus No. 1457



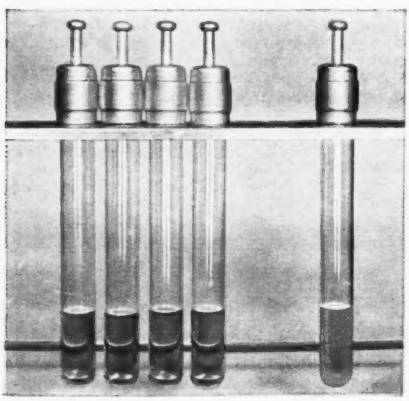
Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
tetracyklin: ingen hämning av bakterieväxten



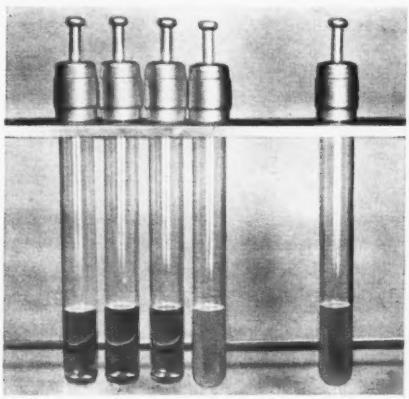
Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
oleandomycin: hämning vid 2.5 γ/ml



Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
oleandomycin: hämning vid 5.0 γ/ml

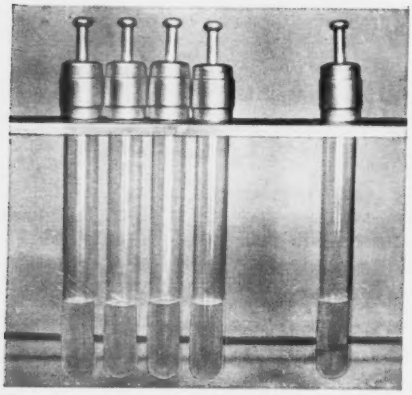


Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
Sigmamycin: hämning i alla spädningar

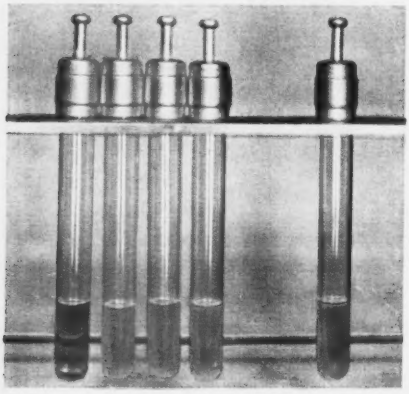


Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
Sigmamycin: hämning vid 1.25 γ/ml

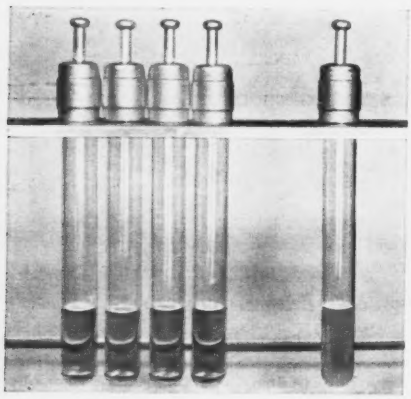
Antibiotika-resistenta bakteriekulturer av M. pyogenes var. aureus No. 1475



Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
tetracyklin: ingen hämning av bakterieväxten

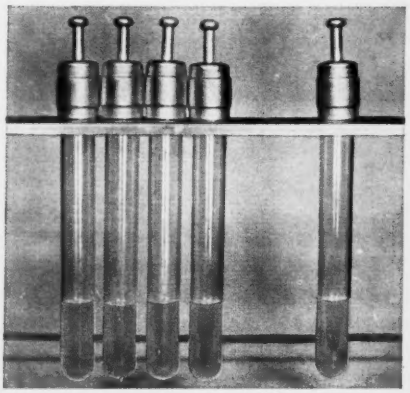


Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
oleandomycin: hämning vid 5.0 γ/ml

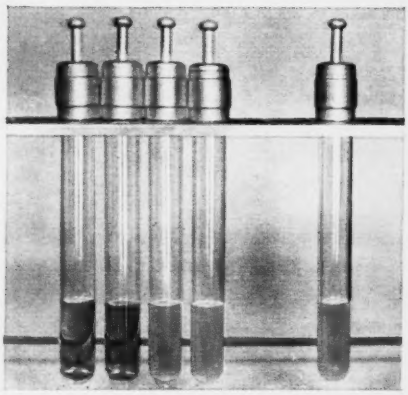


Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
Sigmamycin: hämning i alla spädningar

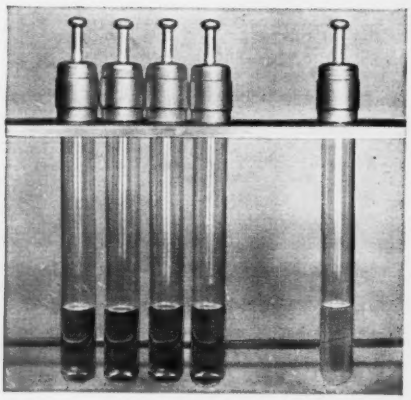
Antibiotika-resistenta bakteriekulturer av M. pyogenes var. No. NB 17



Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
tetracyklin: ingen hämning av bakterieväxten



Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
oleandomycin: hämning vid 2.5 γ/ml



Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
Sigmamycin: hämning i alla spädningar

Sigmamycin

oleandomycin tetracyklin

Tetracyklin och oleandomycin förstärker varandras verkan.
Denna synergistiska effekt visar sig bl. a. i god verkan på stafylokocker och streptokocker. Den fördröjer vidare uppkomsten av antibiotika-resistenta sådana bakterier.
Försök in vitro och in vivo visar god effekt såväl mot stafylokocker som streptokocker, som är resistenta mot andra antibiotika.
Lämpligt för behandling av patienter, hos vilka bredspektrumbehandling är nödvändig och då resistensprövning är svår att genomföra.

Pfizer

Pfizer

Indikationer — Samma som för andra bredspektrum-antibiotika, omfattande infektionssjukdomar, orsakade av ett stort antal mikroorganismer. Dessa omfattar grampositiva och gramnegativa (aeroba och anaeroba) bakterier, rickettsier, spirocheter, stora virus, protozoer och vissa maskar.

Sigmamycin

Dosering — *Vuxna:* 1 kapsel var 6:e timme. Vid svårare infektioner 2 kapslar var 6:e timme.
Större barn: Samma dosering som för vuxna.
Spädbarn och småbarn: 10—20 mg per kg kroppsvikt och dag. Vid svårare infektioner 20—40 mg per kg kroppsvikt och dag. Dagsdosen fördelas på 4 enkeldoser.
Sigmamycin absorberas lätt och adekvata serumkoncentrationer nås hastigt. Fördragbarheten är god och sådana biverkningar, som ses vid användning av andra bredspektrum-antibiotika ses sällan med Sigmamycin.

Förpackningar — Kapslar à 250 mg. Varje kapsel innehåller 83 mg oleandomycin och 167 mg tetracyklin. Glas à 16 och 100 kapslar.

Pfizer Aktiebolag, Stockholm Ö

entre les régions rurales et urbaines. La mortalité des adolescents aux Pays-Bas est favorable, comparé à celle d'autres pays d'Europe occidentale. Une accumulation continue de facteurs favorables conduira à un niveau de trois pour dix milles pour la mortalité des adolescents.

Die Sterblichkeit der Adoleszenten in den Niederlanden.

Die vorliegende Analyse ist eine der ersten speziellen Untersuchungen über die Sterblichkeit von Adoleszenten. Während der letzten 50 Jahre ist die Sterblichkeit von Adoleszenten in den Niederlanden auf ein Siebtel zurückgegangen und hat 5,4 auf zehntausend erreicht (d. h. 7,2 für Knaben und 3,6 für Mädchen). Bei den Mädchen hat die Sterblichkeit viel schneller abgenommen als bei den Knaben. Seit 1930 überflügelt die Sterblichkeit männlicher Adoleszenten die der Mädchen, vor allem infolge höherer Sterblichkeit bei Unfällen der Knaben. Tuberkulose machte in 1920 noch 50 Prozent der totalen Sterblichkeit der Adoleszenten aus, in 1953/54 nur drei Prozent. Sterblichkeit durch Unfälle ist im Verhältnis zur totalen Sterblichkeit dermassen angestiegen, dass auch für dieses Lebensalter Unfälle die hauptsächliche Todesursache sind, wobei Verkehrsunfälle die Hauptrolle spielen. Saisoneinflüsse sind deutlicher nachweisbar als Differenzen zwischen städtischen und ländlichen Gegenden. Im Vergleich mit anderen westeuropäischen Ländern ist die Sterblichkeit der Adoleszenten in den Niederlanden günstig. Eine fortgesetzte Akkumulation günstiger Momente wird dazu führen, dass die Sterblichkeit der Adoleszenten in kurzem auf drei pro zehntausend zurückgehen wird.

Mortalidad de los adolescentes en los Países Bajos.

Este análisis es una de las primeras revisiones especiales realizadas sobre la mortalidad de los adolescentes. Durante los últimos 50 años la mortalidad de los adolescentes en los Países Bajos ha disminuido en un séptimo, alcanzando el 5.4 por diez mil (7.2 para los varones y 3.6 para las hembras). En las muchachas la mortalidad ha diminuido mucho mas aprisa que en los varones. Desde 1930 la mortalidad de los adolescentes varones va detrás de la de las hembras, principalmente por una mayor incidencia de accidentes mortales en los primeros. En 1930 la tuberculosis determinó aun el 50 % de la mortalidad de los adolescentes; en 1953/54 solo el 3 %. La mortalidad por accidentes en relación con la mortalidad total ha aumentado, debiendo señalarse que para esta época de la vida los accidentes son la causa principal de muerte, desempeñando el papel fundamental los accidentes de tráfico. Las influencias estaciones son más claramente comprobables que las diferencias entre los sectores urbanos y rurales. En comparación con otros países del occidente europeo, la mortalidad de los adolescentes en los Países Bajos es favorable. Una continuada acumulación de circunstancias favorables conducirá a que, en corto plazo, la mortalidad de los adolescentes disminuya al tres por diez mil.

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Received August 9, 1956

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Acta Pædiatrica **46**: 249—256. May 1957

From the Royal Manchester Children's Hospital

A Case of Superior Vena Caval Thrombosis Associated with Periarteritis Nodosa

by G. M. KOMROWER, E. U. MACGREGOR and H. B. MARSDEN

Superior vena caval obstruction is a comparatively rare condition, Hinshaw (1949) having estimated its incidence as 1 in 85,000 hospital admissions. By 1949, 600 cases had been described in the world literature, the commonest causes of obstruction being primary and secondary intrathoracic tumours and aortic aneurysm. Only a small number of cases were due to thrombosis, the proportion being variously estimated as 6% (Ehrlich 1934) and 7% (Hinshaw, 1949). The incidence in children is still smaller. Fischer (1904) found only 2% under ten years of age in a series of 252 cases. The series reviewed by Ochsner & Dixon in 1936 consisted of 122 cases of superior vena caval thrombosis, and of these only 3.6% occurred in the first two decades, the youngest patient being nine years of age.

Since 1951 three cases have been described in children. The first was in a girl of two years (Gizsberti Hodenpiyjl, 1951) in whom angiocardiography showed complete obstruction of the superior vena cava with a well-established collateral circulation. This improved spontaneously after one year and was assumed to be inflammatory in origin. In 1954 Muratt & Menano described a boy aged four-and-a-half years with a nephrotic syndrome who developed signs of superior vena caval obstruction three weeks before death, the diagnosis being confirmed at autopsy. They suggested that the thrombosis was associated with the disturbance of plasma proteins possibly aggravated by injections of concentrated albumin, and that infection might also have played a part. In the same year Andersen *et al.* described from Copenhagen three cases of superior vena caval obstruction due to thrombosis. One of these was in a child of nine and is particularly interesting in that it was treated successfully by anastomosis of the azygos vein to the right auricle.

Although Rice *et al.* (1952) published a case of superior vena caval obstruction in a man of 51 years in whom there was a previous illness suggesting rheumatoid arthritis, no description has been found in the literature

of superior vena caval obstruction associated with collagen disease in children and for this reason we are describing the following case which we believe presents such a picture.

Case Report

The patient (R. B.) was first admitted to hospital in November 1949 aged 4 years 9 months suffering from lassitude, pallor and dyspnoea. These symptoms had commenced six months earlier following an attack of whooping cough; in addition the boy complained of intermittent pains in the legs. Four weeks before admission he had suffered from an attack of "croup", followed by tonsillitis and left otitis media. He was given 51 g of sulphonamides in 14 days and then penicillin (0.5 megaunits × 3). On admission there was evidence of anaemia and bronchitis. Radiological examination of the chest: n.a.d. The anaemia was presumed to be due to combined nutritional and infective factors and was responding to oral iron when the patient was discharged.

In February 1952 aged seven years he was seen as an out-patient by one of us (G. M. K.) with a month's history of pains in the feet and purplish marks on the legs. He had suffered from recurrent otorrhoea which had not benefited from tonsillo-adenoidectomy six months previously and since the operation he had lost weight and was lacking in energy. Examination showed a rash on the anterior and posterior aspects of both legs and thighs. It consisted of purplish patches similar to a fading erythema nodosum alternating with irregular brownish staining resembling erythema ab igne.

A week later the patient was admitted to the hospital because of a further attack of otitis media. Investigations showed persistent anaemia (Hb 66 % (9.75 g Hb) with colour index 0.88), together with intermittent polymorphonuclear leucocytosis with eosinophil counts rising as high as 1672 per cu.mm, and a persistently high E.S.R. Plasma proteins totalled 7.69 % with 3.79 % globulin. The otitis media responded to penicillin but intermittent pyrexia persisted and the E.S.R. was still 39 mm five weeks after admission. The skin condition altered very little and was attributed to venous stasis with increased capillary permeability, the aetiology being unknown.

The patient next returned to the hospital in May 1954 when he presented with marked swelling of the face and neck first noticed six weeks previously. Examination revealed marked distension of the superficial veins of the face, neck, thorax, and abdominal wall together with oedema of the face and neck. There was no cyanosis at rest but definite cyanosis and dyspnoea on exertion. A diagnosis of superior vena caval obstruction was made and later confirmed by phlebography, the dye entered the superior vena cava but did not outline the azygos vein. Radiological examination including tomography failed to reveal a mediastinal tumour. There was an intermittent pyrexia, E.S.R. was 46 mm, blood count and urine examinations were normal, Wassermann reaction and Mantoux test (1 in 10 O.T.) negative. A tentative diagnosis of superior vena caval thrombosis secondary to low-grade mediastinitis was made and the patient treated with chlortetracycline for a fortnight. On this treatment his temperature settled and his E.S.R. fell from 46 to 13 mm. He was discharged home on 17th July. During the next six months the anastomotic channels on the neck and chest became more pronounced and the swelling of face and neck diminished. Blood counts were very variable but there was always a slight anaemia and intermittently an eosinophilia. Urine showed no abnormality on repeated examination.

The patient was re-admitted on 27th February, 1955, at the age of 10 years with

right-sided abdominal pain, anorexia and nausea. Examination suggested low-grade appendicitis and this was confirmed at laparotomy, the appendix which was removed showing signs of old and recent inflammation. Laparotomy also revealed a mass of small matted glands at the upper end of the aorta and in the mesentery of the ileum. One was removed for section and showed only non-specific, chronic inflammation. Post-operative recovery was uneventful but the boy's general condition remained poor and there was still fullness of the face and neck with dilatation of superficial veins. Investigations during the next three months showed a persistent, normochromic anaemia, some albumin and red cells in his urine and a persistently high E.S.R. Mantoux was still negative and X-ray chest showed no significant change. Electrophoresis of plasma protein showed some increase in globulin but no other abnormality. Skin and muscle biopsy were negative. Sarcoidosis, toxoplasmosis and amyloidosis were excluded by appropriate investigations. Venous pressures in the supine position were shown to be 14.5 cm sodium citrate in the left saphenous vein at the ankle and 25 cm in the left antecubital fossa (15 cm being considered the upper limit of normal). The patient's condition deteriorated steadily and he lost nearly 5 lbs in weight in six weeks. A course of chlortetracycline this time produced no improvement in general condition or fall in E.S.R. and it was therefore replaced by oxytetracycline. After eleven days there was some improvement and he was discharged home on 13th May on small doses of oxytetracycline (100 mg daily) and vitamin B supplement.

He returned to hospital two and a half weeks later when he complained of nausea, anorexia, extreme weakness and abdominal pain. He was anaemic, Hb 46 % (6.89 g Hb), and the E.S.R. was 148 mm. The urine repeatedly contained albumin and red cells. Cortisone and oxytetracycline were given but his blood pressure began to climb (160/110) and clinical signs of uraemia supervened. His general condition slowly deteriorated and he went into coma and died on Sept. 11th, 1955.

Post-mortem Examination (Dr. H. B. Marsden)

Summary of findings.—Organized thrombus in the superior vena cava. Periarteritis involving the liver, spleen and gastro-intestinal tract with necrotizing glomerulitis in the kidney. Pleural, pericardial and peritoneal adhesions. Bronchopneumonia.

External appearances.—The body showed wasting and the superficial veins on the left side of the chest were unduly prominent.

Gross findings.—THORAX: There were extensive fibrous pleural and pericardial adhesions and the lungs showed oedema and consolidation. Organized thrombus obstructed the superior vena cava at its origin. The azygos vein was dilated and engorged.

ABDOMEN: Numerous chronic adhesions were seen between the viscera particularly in the region of the liver. Rounded grey areas up to 4 mm in diameter were present in the spleen and liver and some of the vessels in the latter were occluded by hyaline material.

The kidneys were shrunken and pale with granular surfaces covered with petechiae. There was narrowing of the cortical strips and the latter had a grey speckled appearance with loss of normal vascular markings.

The *remainder of the examination* was essentially negative.

Microscopic appearance.—The *lung* showed intense bronchopneumonic reaction with acute inflammatory cells and oedema fluid in the alveoli.

In the *spleen* there was thickening of the capsule and the trabeculae were prominent. The follicular arterioles showed recent and chronic inflammatory lesions with fibrinoid necrosis and polymorphonuclear infiltration in some places and obliteration with

of superior vena caval obstruction associated with collagen disease in children and for this reason we are describing the following case which we believe presents such a picture.

Case Report

The patient (R. B.) was first admitted to hospital in November 1949 aged 4 years 9 months suffering from lassitude, pallor and dyspnoea. These symptoms had commenced six months earlier following an attack of whooping cough; in addition the boy complained of intermittent pains in the legs. Four weeks before admission he had suffered from an attack of "croup", followed by tonsillitis and left otitis media. He was given 51 g of sulphonamides in 14 days and then penicillin (0.5 megaunits × 3). On admission there was evidence of anaemia and bronchitis. Radiological examination of the chest: n.a.d. The anaemia was presumed to be due to combined nutritional and infective factors and was responding to oral iron when the patient was discharged.

In February 1952 aged seven years he was seen as an out-patient by one of us (G. M. K.) with a month's history of pains in the feet and purplish marks on the legs. He had suffered from recurrent otorrhoea which had not benefited from tonsillo-adenoidectomy six months previously and since the operation he had lost weight and was lacking in energy. Examination showed a rash on the anterior and posterior aspects of both legs and thighs. It consisted of purplish patches similar to a fading erythema nodosum alternating with irregular brownish staining resembling erythema ab igne.

A week later the patient was admitted to the hospital because of a further attack of otitis media. Investigations showed persistent anaemia (Hb 66 % (9.75 g Hb) with colour index 0.88), together with intermittent polymorphonuclear leucocytosis with eosinophil counts rising as high as 1672 per cu.mm, and a persistently high E.S.R. Plasma proteins totalled 7.69 % with 3.79 % globulin. The otitis media responded to penicillin but intermittent pyrexia persisted and the E.S.R. was still 39 mm five weeks after admission. The skin condition altered very little and was attributed to venous stasis with increased capillary permeability, the aetiology being unknown.

The patient next returned to the hospital in May 1954 when he presented with marked swelling of the face and neck first noticed six weeks previously. Examination revealed marked distension of the superficial veins of the face, neck, thorax, and abdominal wall together with oedema of the face and neck. There was no cyanosis at rest but definite cyanosis and dyspnoea on exertion. A diagnosis of superior vena caval obstruction was made and later confirmed by phlebography, the dye entered the superior vena cava but did not outline the azygos vein. Radiological examination including tomography failed to reveal a mediastinal tumour. There was an intermittent pyrexia, E.S.R. was 46 mm, blood count and urine examinations were normal, Wassermann reaction and Mantoux test (1 in 10 O.T.) negative. A tentative diagnosis of superior vena caval thrombosis secondary to low-grade mediastinitis was made and the patient treated with chlortetracycline for a fortnight. On this treatment his temperature settled and his E.S.R. fell from 46 to 13 mm. He was discharged home on 17th July. During the next six months the anastomotic channels on the neck and chest became more pronounced and the swelling of face and neck diminished. Blood counts were very variable but there was always a slight anaemia and intermittently an eosinophilia. Urine showed no abnormality on repeated examination.

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right-sided abdominal pain, anorexia and nausea. Examination suggested low-grade appendicitis and this was confirmed at laparotomy, the appendix which was removed showing signs of old and recent inflammation. Laparotomy also revealed a mass of small matted glands at the upper end of the aorta and in the mesentery of the ileum. One was removed for section and showed only non-specific, chronic inflammation. Post-operative recovery was uneventful but the boy's general condition remained poor and there was still fullness of the face and neck with dilatation of superficial veins. Investigations during the next three months showed a persistent, normochromic anaemia, some albumin and red cells in his urine and a persistently high E.S.R. Mantoux was still negative and X-ray chest showed no significant change. Electrophoresis of plasma protein showed some increase in globulin but no other abnormality. Skin and muscle biopsy were negative. Sarcoidosis, toxoplasmosis and amyloidosis were excluded by appropriate investigations. Venous pressures in the supine position were shown to be 14.5 cm sodium citrate in the left saphenous vein at the ankle and 25 cm in the left antecubital fossa (15 cm being considered the upper limit of normal). The patient's condition deteriorated steadily and he lost nearly 5 lbs in weight in six weeks. A course of chlortetracycline this time produced no improvement in general condition or fall in E.S.R. and it was therefore replaced by oxytetracycline. After eleven days there was some improvement and he was discharged home on 13th May on small doses of oxytetracycline (100 mg daily) and vitamin B supplement.

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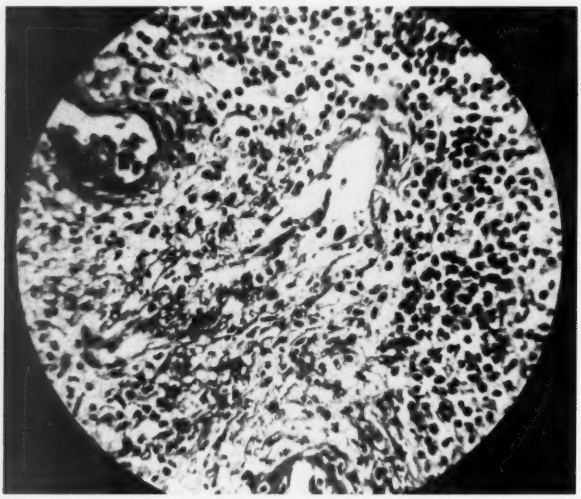

Fig. 1. Photomicrograph of a Malpighian body showing central necrosis with polymorphonuclear infiltration and connective tissue proliferation. (H. and E. High Power.)

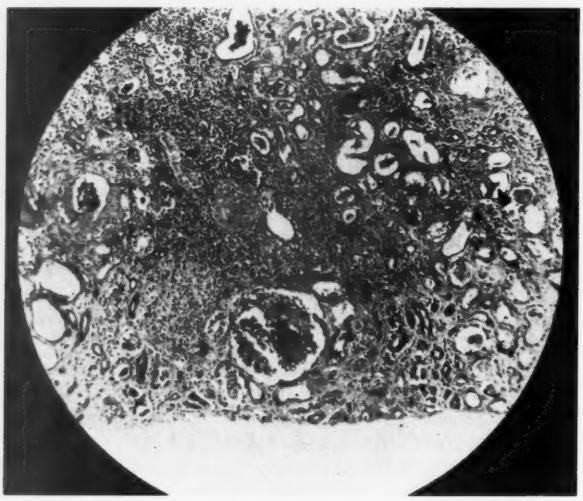

Fig. 2. Low-power view of the kidney showing fibrosis, chronic inflammatory reaction and atrophy of tubular cells. One glomerulus shows necrotizing glomerulitis with fibrinoid necrosis of the tufts. (H. and E.)

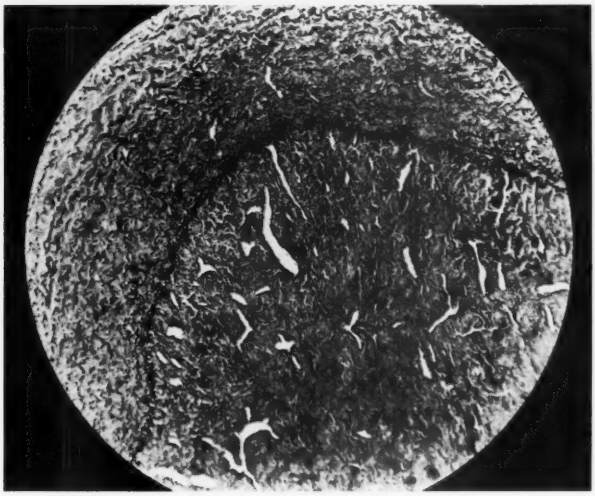

Fig. 3. Photomicrograph of the superior vena cava showing obliteration of the lumen by connective tissue with numerous recanalized channels. The elastic tissue in the wall is well preserved. (Weigert–van Gieson. Low Power.)

fibrosis in others. Necrosis of Malpighian bodies with polymorphonuclear infiltration was a prominent feature while other follicles showed fibrous replacement. The picture was similar to that described by Ball & Davson (1949) in periarteritis nodosa (Fig. 1).

The *kidney* was severely damaged, the majority of glomeruli showing evidence of scarring while many were converted into balls of fibrous tissue. In addition, necrotizing glomerulitis with fibrinoid necrosis and polymorphonuclear infiltration of the tufts could be seen. The appearances resembled those described by Wainwright & Davson (1950) in the microscopic form of periarteritis nodosa (Fig. 2). Interstitial fibrosis and chronic inflammatory reaction were extensive. The epithelium of the convoluted tubules was flattened and the lumina were dilated by eosinophilic, leucocytic and red cell casts. Little evidence of vascular damage could be detected and the collecting tubules and pelvic epithelium were intact.

There was evidence of both recent and old vascular injury in the *liver* with necrosis and polymorphonuclear invasion of the arterial walls in addition to fibrosis and chronic inflammatory reaction of other vessels.

The *stomach* and *terminal ileum* showed a similar picture of acute and chronic inflammation in the serosal vessels.

In the *superior vena cava* there was obliteration of the original lumen by fibrous tissue with small re-canalized channels (Fig. 3). The internal elastic lamina and muscle wall could still be detected in some places. There was extensive surrounding fibrosis with no cellular infiltration.

Examination of the *brain* showed amoeboid transformation of glial cells with scanty lymphocytic meningeal infiltration.

Bacteriology.—Cultures were taken from the heart blood, lung, superior vena cava, liver and intestinal wall: There was a growth of Staphylococcus pyogenes from the lung, the other cultures being sterile.

Discussion

The long history with the initial anaemia, high E.S.R. and temporary renal involvement with the persistent eosinophilia can all be explained on the basis of a hypersensitivity state; the unusual nodal erythema has been found in a case of periarteritis nodosa described by Klotz in 1917 and one of the authors (G. M. K.) has more recently seen a small boy with rheumatoid arthritis in whom the presenting sign was a nodal erythema. The nature and distribution of the lesions are very similar to those described by Zeek (1953) in her paper on necrotizing angiitis under the sub-heading *periarteritis nodosa*: in addition the microscopic findings in the kidney, spleen and vessels of the gastro-intestinal tract establish this diagnosis. There is no family history of allergic disorders but the boy had suffered in infancy from repeated attacks of bronchitis associated with teething and there is a story of an attack of croup one month before his first admission in 1949.

Hinshaw (1949) stated that obstructions are more serious when they are situated below the insertion of the azygos vein and that obstructions of the superior vena cava above this point may be tolerated for a long time. The findings in our case support these conclusions: the obstruction itself provided little disability once an adequate collateral circulation had developed and death resulted from uraemia following an exacerbation of the renal lesion.

Although small arteries and arterioles are usually affected in periarteritis nodosa there is increasing evidence of venous involvement (Zeek, 1952). It is, therefore, possible that there was a primary involvement of the vena cava in this case although no evidence of active phlebitis was detected elsewhere in the body; in some areas of chronic vascular scarring, however, notably in the liver, it was not possible to say whether arteries or veins had been affected. Alternatively, the initial lesion may have been situated in the vasa-vasorum of the vena cava and was subsequently obliterated by the low-grade inflammation which produced the thrombosis. Either of these hypotheses could account for some of the cases of primary thrombosis listed by Hinshaw (1949). Finally, the vena caval obstruction may have arisen as the result of a mediastinitis, as there was evidence of widespread old inflammation in the pericardium, mediastinal and parietal pleurae and peritoneum. The occurrence of polyserositis in periarteritis nodosa has been described by a number of authors including Ophuls (1923), who reported a case with extensive involvement of the serous membranes.

There are three possible aetiological factors: firstly, the sulphonamides that were given in 1949 during the initial attack of otitis media; secondly, the penicillin that was given at that time and was prescribed again in 1952 when the boy had a streptococcal pharyngitis. (These drugs together with phenytoin and thiouracil are included in the group of drugs indicated as antigens and responsible for the vascular lesions of periarteritis nodosa (Rich, 1942)). Finally, the otitis media itself which recurred on several occasions during the next five years: the only swab from the ear was taken in 1952 and pneumococci were grown. It is possible that this was not the initial infecting organism which may well have been a streptococcus and that the latter was the sensitising agent.

We believe that the entire clinical history and pathological picture in this case can be explained on the basis of a hypersensitivity phenomenon such as periarteritis nodosa and we present it as an example of one possible aetiological factor in cases of superior vena caval obstruction said to be due to a primary thrombosis or a mediastinal fibrosis.

Summary

1. A case of superior vena caval thrombosis is described in a child of nine years.

2. The clinical progress suggested the possibility of a necrotizing angiitis and autopsy examination disclosed a periarteritis nodosa.

3. The relationship of periarteritis nodosa and superior vena caval thrombosis due to "non-specific mediastinitis" is discussed.

We are most grateful to Professor A. C. P. Campbell, Professor of Pathology, University of Manchester, for his criticism and advice.

Un cas de thrombose dans la veine cave supérieure, associée avec une périartérite noueuse.

Un cas de thrombose de la veine cave supérieure chez un enfant de 9 ans, est décrit. La progression clinique a suggéré la possibilité d'une angiite nécrotique et l'autopsie a révélé une périartérite noueuse. Le rapport existant entre la périartérite noueuse et la thrombose de la veine cave supérieure dûe à une « médiastinite non spécifique », est développé.

Ein Fall von Thrombose der oberen Hohlvene in Zusammenhang mit Periarteriitis nodosa.

Thrombose der Vena cava superior bei einem 9jährigen Kind ist beschrieben. Der klinische Verlauf wies auf die Möglichkeit einer nekrotisierenden Angioitis hin, und die Autopsie enthüllte die Anwesenheit einer Periarteriitis nodosa. Die Beziehung von Periarteriitis nodosa zur Thrombose der oberen Hohlvene infolge einer „unspezifischen Mediastinitis" wird einer Erörterung unterzogen.

Un caso de trombosis en la vena cava superior, asociada con periarteritis nodular.

Descríbese un caso de trombosis en la vena cava superior de un niño de 9 años de edad. La progresión clínica sugirió la posibilidad de angiítis necrótica, y la autopsia reveló periarteritis nodular. Discútese la relación existente entre la periarteritis nodular y la trombosis en la vena cava superior debida a "mediastinitis no específica".

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Received Nov. 13, 1956

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Acta Pædiatrica **46**: 257—264. May 1957

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Vergleichende Untersuchung zur Aminosäurenzusammensetzung des Gerüsteiweißes von Nabelschnur- und Erwachsenenerythrozytenstromaten[1]

von WILHELM KÜNZER und ERICH SCHÜTZ

Wie aus zahlreichen Veröffentlichungen hervorgeht, unterscheiden sich *Nabelschnur*erythrozyten durch zahlreiche wesentliche *Eigenheiten* von *Erwachsenen*erythrozyten. So wußte man schon lange, daß die Blutfarbstoffbeladung der beiden Zellpopulationen different ist. Nabelschnurerythrozyten enthalten ganz vorwiegend fetales Hämoglobin (Hb F), Erwachsenenerythrozyten hingegen bleibendes Hämoglobin (Hb A) (4). Neue Untersuchungen zeigten, daß Unterschiede hinsichtlich der erythrozytären Fermentsysteme bestehen. Die Aktivität von Katalase, Cholinesterase, Glyoxalase, Carboanhydrase und der Reduktionssysteme ist in Nabelschnurerythrozyten erheblich geringer als in Erwachsenenerythrozyten (9, 11, 12). Auch im Verhalten gegen oxydative Gifte (Natriumnitrit, Kaliumchlorat, *p*-Aminophenol, Dinitroglykol u.a.) kamen bedeutungsvolle Abweichungen zum Vorschein. In Nabelschnurerythrozyten gehen sowohl die reversiblen Oxydationen am Hämoglobineisen (Hämiglobinbildung) als auch die irreversiblen Oxydationen an der Zelle (Heinzkörperbildung) wesentlich leichter vor sich als in Erwachsenenerythrozyten (13, 14). Die Brunnenwasser- und Stempelfarbenblausucht (2, 3) sowie die sog. „spontane Heinzkörperbildung" bei Frühgeburten, Neugeborenen und jungen Säuglingen (6, 15) sind sichtbarer Ausdruck dieses verminderten Oxydationsschutzes. Außerdem zeigen die Nabelschnurerythrozyten hinsichtlich Lebensdauer (8, 16), äußerer Gestalt (20) sowie osmotischer und mechanischer Resistenz (21) grobe Abweichungen vom Verhalten der Erwachsenenerythrozyten.

Aus diesen Tatsachen darf gefolgert werden, daß grundlegende Strukturunterschiede zwischen Nabelschnur- und Erwachsenenerythrozyten bestehen. Wir fragten uns, ob diese Differenzen auch den Aufbau des *Stromaei-*

[1] Mit Unterstützung der Deutschen Forschungsgemeinschaft.

weißes betreffen und untersuchten vergleichend die Aminosäurenzusammensetzung der Stromata von Nabelschnur- und Erwachsenenerythrozyten.

In der Literatur liegen über die Aminosäurenzusammensetzung von Nabelschnurerythrozytenstromata keine Untersuchungen vor und bei Erwachsenenerythrozytenstromata wurden — soweit wir sehen — lediglich die Aminosäuren Histidin, Arginin, Lysin, Tyrosin, Tryptophan, Cystin und Methionin quantitativ bestimmt (1).

Methodik

Zur Darstellung hämoglobinfreier Erythrozytenstromata folgten wir weitgehend den Angaben von Tishkoff, Robscheit-Robbins und Whipple (23). Einzelheiten finden sich an anderer Stelle (18). Für die Hydrolyse des Stromas und die Bestimmung der Aminosäuren im Hydrolysat hielten wir uns an die allgemeinen für quantitative Aminosäurenbestimmung ausgearbeiteten Bedingungen (5).

a) *Gewinnung der Erythrozytenstromata:*

Die gewaschenen Erythrozyten wurden in Aqua dest. hämolysiert und mit 0,02 m Azetatpufferlösung vom pH 4,6 ausgeflockt. Nach Sedimentieren der Stromata wurde der Überstand abgesaugt und mit verdünntem Eisessig (1:10 000) aufgefüllt. Nach abermaligem Stehenlassen wurde das Sediment zentrifugiert, der Überstand dekantiert und die Stromata nochmals mit verdünntem Eisessig (1:10 000) gewaschen. Alle Arbeitsgänge erfolgten bei Eisschranktemperatur. Die gewonnenen Stromaten wurden dann in Alkohol–Äther und weiter in Chloroform–Methanol extrahiert.

b) *Hydrolyse:*

Die von Hämoglobin befreiten und extrahierten Stromaten trockneten wir im Hochvakuum über Phosphorpentoxyd und Natriumhydroxyd bis zur Gewichtskonstanz. 5–10 mg der fein verriebenen Substanz wurden in Glasröhrchen mit einem Gemisch aus 6 n HCl und 90%iger Ameisensäure übergossen, unter Stickstoff abgeschmolzen und 24 Stunden bei 100°C hydrolysiert. Nach Öffnen führten wir die Menge quantitativ in ein 10 cm^3 Erlenmeyer-Schliffkölbchen über und trockneten erneut über Phosphorpentoxyd und NaOH bei 14–16 Torr. bis zur Gewichtskonstanz ein. Daraufhin wogen wir auf der Mikrowaage 1,0 g Aqua dest. hinzu und fügten einen Tropfen Toluol bei. Die Hydrolysate waren also 0,5–1%ig und wurden bis zur Trennung der Aminosäuren auf dem Papier im Eisschrank aufbewahrt.

c) *Papierchromatographie:*

Wir folgten hier eng den Angaben von Fischer und Dörfel, auf welche wir ausdrücklich verweisen (5). Die Aminosäurengemische wurden strichförmig auf vorbereitetes Whatman-Papier Nr. I aufgetragen und durch eindimensionale Chromatographie absteigend mit — für die einzelnen Aminosäuren geeigneten — Lösungsmitteln entwickelt. (Phenol pH 12 trennte: Asparaginsäure, Glutaminsäure, Serin, Glykokoll,

Threonin, Alanin, Tyrosin; Phenol pH 1 trennte: Cystin, Alanin, Tyrosin, Valin, Methionin; Lutidin pH 6,2 trennte: Arginin, Lysin; *o*-Kresol pH 6,2 trennte: Phenylalanin; *n*-Butanol pH 8,4 trennte: Isoleucin, Leucin.) Nach Trocknung ließen wir die Papierstreifen mit Ninhydrin reagieren und führten die aus den einzelnen Aminosäuren gebildeten Farbstofflecke durch Aufsprühen einer Kupfernitratlösung in die entsprechenden Kupferkomplexe über. Diese wurden in Methanol gelöst und ihre Konzentration spektrophotometrisch gemessen.

Zur Eichung der Werte läuft auf dem Papier normalerweise ein Gemisch aus bekannten Mengen der zu bestimmenden Aminosäuren mit (5). Statt dessen haben wir bei unseren Untersuchungen die Aminosäuren aus Nabelschnur- und Erwachsenenerythrozytenstromata nebeneinander wandern lassen. Da die Gemische sehr ähnlich zusammengesetzt waren und unter gleichen Versuchsbedingungen entwickelt, besprüht und getrocknet wurden, konnten für gleiche Aminosäuren die gemessenen Farbintensitäten der Kupfersalzlösungen aufeinander bezogen werden. Der Quotient der Extinktionen drückt das Mengenverhältnis der Aminosäuren in Nabelschnur- und Erwachsenenerythrozytenstromata aus. Bei gleichen Aminosäurenmengen ist der Quotient gleich eins, bei ungleichen größer oder kleiner. Die Erwachsenenerythrozytenwerte wurden stets durch die Nabelschnur-erythrozytenwerte geteilt. Die Fehlerbreite der Methode hat sich mit $\pm 5\,\%$ ergeben.

Abweichend hiervon bestimmten wir Histidin nach der Methode von MacPherson (19), Tryptophan und Tyrosin nach den Angaben von Goodwin und Morton (7). Die Fehlerbreite der Bestimmungsmethode für Histidin beträgt $\pm 2\,\%$, für Tryptophan und Tyrosin $\pm 5\,\%$.

Ergebnisse

Unsere Resultate finden sich in der Tab. 1. Den Werten kann ohne weiteres entnommen werden, daß die gemittelten Quotienten nur geringfügig von eins abweichen. *Es ergeben sich daher in der Aminosäurenzusammensetzung von Nabelschnur- und Erwachsenenerythrozytenstromata grob gesehen keine Unterschiede.* Um festzustellen, ob nicht dennoch eine signifikante Differenz besteht, haben wir die K-Werte für die bestimmten Aminosäuren nach der Formel $K = (M_1 - M_2)/\sqrt{\varepsilon_1^2 + \varepsilon_2^2}$ berechnet (22). Aus Tab. 2 gehen die Ergebnisse der Berechnung hervor. Da alle K-Werte kleiner als zwei sind, bestehen keine signifikanten Unterschiede. Die statistische Berechnung bestätigt also den ersten Eindruck. Der Aufbau des Stromaeiweißes von Nabelschnur- und Erwachsenenerythrocyten weist — was Art und Menge der Aminosäuren anbelangt — *keine* gesicherten Unterschiede auf.

Einschränkend muß allerdings gesagt werden, daß diese Aussage nicht für alle Aminosäuren gilt, weil wir nur 17 der bekannten Aminosäuren bestimmten. So wurden Prolin und Oxyprolin wegen methodischer Schwierigkeiten nicht untersucht. Die zur Zeit üblichen chromatographischen quantitativen Methoden für diese Aminosäuren weisen noch eine erhebliche Schwankungsbreite auf, so daß evt. geringe Differenzen nicht deutlich hätten werden können. Gröbere Unterschiede sind in diesem Zusammenhang jedoch ebenfalls unwahrscheinlich.

TABELLE

Vergleich der Aminosäurenzusammensetzung von Stromaeiweiß

Gebildet wurde der Quotient aus den Extinktionen der Kupferkomplex-

Nr.	Asparaginsäure	Glutaminsäure	Serin	Glykokoll	Threonin	Alanin	Tyrosin	Phenylalanin
1	1,12	0,95	1,09	1,01	1,00	0,99	0,45	1,05
2	0,77	0,97	0,99	0,94	0,81	1,09	0,68	1,19
3	0,98	0,99	0,91	1,11	1,58	0,82	1,00	0,87
4	0,96	1,00	0,97	1,06	1,02	1,06	0,94	1,00
5	0,86	1,04	0,71	0,88	0,97	1,09	1,19	0,72
6	1,00	0,96	1,05	0,97	1,13	1,13	1,23	1,09
7	0,92	1,03	0,96	0,80	1,53	1,04	1,09	1,44
8	0,86	0,99	1,13	1,65	1,07	1,17	1,28	1,08
9	0,96	1,00	1,31	1,18	1,17	1,10	1,09	1,21
10	1,03	0,94	0,67	1,21	1,41	1,03	0,92	0,99
11	1,00	0,99	0,85	2,92	1,14	0,93	1,10	1,46
12	1,13	0,88	1,00	0,89	0,97	1,09	1,00	1,04
13	1,07	0,96	1,21	1,18	0,88	0,88	1,00	1,16
14	1,02	0,93	0,91	1,03	0,48	1,03	1,08	0,68
15	0,91	0,85	0,64	0,86	1,17	0,79	0,92	1,25
16	0,77	1,12	1,18	1,06	0,98	0,99	1,00	1,11
17	1,10	0,97	1,00	1,04	1,02	0,98	1,15	0,82
18	0,90	0,90	1,15	0,97	0,92	1,04	0,97	1,20
19	1,11	1,11	1,14	1,08	1,00	1,07	0,77	1,11
20	0,95	1,04	1,10	0,95	0,99	1,03	0,95	1,28
21	0,94	1,12	1,08	0,74	0,88	1,12	0,92	0,75
22	1,00	0,96	0,91	0,98	1,08	0,82	0,60	2,12
23	1,03	0,90	0,90	1,11	0,79	1,07	1,18	0,94
24	1,03	1,00	1,04	0,93	0,88	1,14	1,05	0,87
25	0,98	1,04	0,99	1,10	1,00	0,98	0,87	1,00
26	0,97	0,91	1,01	0,81	0,89	0,96	0,99	0,81
27	1,05	0,99	0,92	0,89	1,00	1,05	0,87	0,95
28	0,83	0,88	0,63	0,67	0,90	0,98	0,81	0,88
29	1,15	1,14	1,50	1,44	0,97	1,07	1,02	0,87
30	0,89	0,76	0,93	0,78	0,62	1,00	1,09	1,04
31	0,87	0,78	0,91	0,89	1,54	0,95	0,80	—
32	0,70	0,66	0,57	1,03	0,91	1,11	1,06	—
33	0,63	0,79	0,87	0,70	0,77	1,00	1,17	—
34	1,06	0,77	1,04	0,93	0,70	0,99	0,66	—
35	0,89	1,00	1,16	1,00	0,73	1,03	1,19	—
36	—	—	—	—	—	0,66	0,70	—
37	—	—	—	—	—	1,19	0,89	—
38	—	—	—	—	—	0,70	0,80	—
39	—	—	—	—	—	0,89	0,86	—
40	—	—	—	—	—	0,80	1,16	—
41	—	—	—	—	—	0,86	0,51	—
42	—	—	—	—	—	1,16	0,91	—
43	—	—	—	—	—	0,51	0,64	—
44	—	—	—	—	—	0,91	1,52	—
45	—	—	—	—	—	0,64	0,85	—
46	—	—	—	—	—	1,52	0,78	—
47	—	—	—	—	—	0,84	0,91	—
48	—	—	—	—	—	0,78	0,71	—
49	—	—	—	—	—	0,91	0,84	—
50	—	—	—	—	—	0,71		—
51	—	—	—	—	—	0,84		—
M	0,96	0,95	0,98	1,05	1,00	0,97	0,94	1,07

1

aus Nabelschnurerythrozyten und Erwachsenenerythrozyten.

lösungen der Aminosäuren aus Nabelschnur- und Erwachsenenstromata.

Cystin	Valin	Methionin	Leucin	Isoleucin	Lysin	Arginin	Tryptophan	Histidin
1,06	0,96	1,03	1,24	0,99	0,72	0,62	0,61	0,91
0,88	1,12	0,95	0,55	0,95	0,52	1,64	0,61	0,88
1,06	1,03	0,89	1,08	0,72	0,54	0,92	0,67	0,93
1,08	1,06	1,14	1,06	1,02	0,67	0,93	0,66	0,87
1,74	1,20	0,91	0,98	0,86	0,85	0,93	0,63	0,90
0,86	0,86	0,64	0,73	1,24	1,15	0,93	0,64	1,01
1,07	1,01	0,94	0,91	0,92	1,17	1,07	0,65	0,92
0,69	1,03	1,16	0,70	0,98	1,23	0,95	0,63	0,93
0,92	0,89	1,06	0,89	0,46	1,05	0,92	0,64	0,95
1,22	1,11	1,02	0,84	1,30	1,08	1,03	0,67	0,88
1,00	1,07	0,85	0,80	0,95	1,00	1,12	0,89	1,11
1,10	1,07	0,93	0,89	0,97	0,95	1,15	0,99	1,08
0,89	0,88	0,52	1,78	1,46	0,99	1,00	0,97	1,25
0,86	1,13	0,97	0,73	1,10	0,94	1,00	1,00	1,10
0,76	0,96	1,12	0,93	1,33	0,91	0,93	0,92	1,08
0,97	1,00	1,24	0,79	1,78	1,27	0,93	0,93	0,98
1,06	1,07	1,06	0,71	0,53	1,00	1,16	0,98	0,99
1,05	1,14	1,12	—	—	1,08	—	0,96	0,94
0,92	1,27	0,94	—	—	0,93	—	0,98	0,93
0,68	0,87	0,69	—	—	0,82	—	1,02	0,88
0,92	0,83	0,71	—	—	—	—	1,03	1,09
0,75	0,97	0,89	—	—	—	—	1,03	0,99
0,60	0,79	0,84	—	—	—	—	1,07	0,93
0,89	0,97	0,83	—	—	—	—	1,14	0,89
0,91	0,94	0,86	—	—	—	—	1,07	0,95
0,83	0,95	0,87	—	—	—	—	1,08	0,94
0,74	0,93	—	—	—	—	—	1,09	0,93
—	—	—	—	—	—	—	1,08	0,94
—	—	—	—	—	—	—	1,04	0,97
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
0,94	1,00	0,93	0,92	1,03	0,94	1,01	0,88	0,97

TABELLE 2

Vergleich der Aminosäurenzusammensetzung der Stromata aus Nabelschnur- und Erwachsenenblut. Statistische Berechnung nach L. Ther (22).

Aminosäuren	Mittelwerte	ε in %	K-Werte
Asparaginsäure	0,96	±2,0	0,74
Glutaminsäure	0,95	±1,9	0,94
Serin	0,98	±3,3	0,34
Glykokoll	1,05	±6,0	0,62
Threonin	1,00	±4,5	0,00
Alanin	0,97	±2,5	0,54
Tyrosin	0,94	±3,2	1,03
Phenylalanin	1,07	±4,7	0,99
Cystin	0,94	±4,4	0,93
Valin	1,00	±2,2	0,00
Methionin	0,93	±3,6	1,17
Leucin	0,92	±7,2	0,97
Isoleucin	1,03	±7,6	0,32
Thryptophan	0,88	±4,0	1,97
Histidin	0,97	±1,6	1,20
Lysin	0,94	±4,9	0,88
Arginin	1,01	±4,9	0,14

Diskussion

Kürzlich konnten wir zeigen, daß für die Heinzkörperbildung die Anwesenheit von Hämoglobin in der Zelle *nicht* unbedingt erforderlich ist. Mittels oxydativer Noxen ließen sich nämlich Heinzkörper auch an hämoglobinfreien Erythrozytenstromata erzeugen (17).

Als wir daraufhin vergleichende Untersuchungen durchführten, entstanden die Heinzkörper an Stromata von Nabelschnurerythrozyten bedeutend leichter als an Stromata von Erwachsenenerythrozyten. Wir folgerten daraus, daß *Strukturunterschiede zwischen den Membranen von Nabelschnur- und Erwachsenenerythrozyten bestehen müßten*, was auch schon die eingangs dargelegten Gründe nahelegten.

Unsere oben beschriebenen Untersuchungen liefern hierfür allerdings keine weiteren Anhaltspunkte. Es ergibt sich vielmehr, daß *die Aminosäurenzusammensetzung von Nabelschnurerythrozytenstromata in qualitativer und quantitativer Hinsicht derjenigen von Erwachsenenerythrozytenstromata entspricht.* Unter normalen Verhältnissen scheint also die Aminosäurenzusammensetzung des Stromaeiweißes im Verlaufe des Lebens keinen faßbaren Veränderungen zu unterliegen. Trotzdem kann sich natürlich die Feinstruktur des Stromaeiweißes erheblich wandeln, allein schon durch verschiedene

Anordnung der Aminosäuren im Proteinmolekül. Insofern könnte die oben beschriebene, unterschiedliche Reaktionsweise von Neugeborenen- und Erwachsenenerythrozyten möglicherweise doch auf das Gerüsteiweiß bezogen werden. Weitere Untersuchungen zur Klärung dieser Frage sind erforderlich.

Als Beispeil für das Bestehen feinstruktureller Unterschiede im Aminosäurenaufbau sei auf den menschlichen Blutfarbstoff verwiesen. Das Hämoglobin E weicht hinsichtlich mehrerer physikalisch-chemischer Eigenschaften vom Erwachsenenhämoglobin ab, obgleich die Aminosäurenzusammensetzung beider Globine identisch ist und Differenzen zwischen den Hämanteilen nicht bestehen (10).

Zusammenfassung

Die Aminosäurenzusammensetzung des Gerüsteiweißes von Nabelschnurerythrozytenstromaten weicht weder in qualitativer noch in quantitativer Hinsicht von derjenigen des Gerüsteiweißes von Erwachsenerythrozytenenstromaten ab.

Comparative Study on the Composition of Amino-acids in the Stroma-proteins of the Erythrocytes in the Umbilical Cord and Those of the Adult.

The composition of amino-acids in the stroma-proteins of red blood corpuscles in the umbilical cord is neither qualitatively nor quantitatively different from that of the stroma-proteins in adult erythrocytes.

Etude comparée de la composition des amino-acides des albuminoïdes du stroma érythrocytaire du cordon ombilical et des érythrocytes d'adultes.

La composition des amino-acides des albuminoïdes du stroma érythrocytaire du cordon ombilical et des adultes ne diffère ni qualitativement ni quantitativement.

Estudio comparativo entre la constitución aminoácida del armazón proteico del estroma eritrocitario del adulto y el del estroma eritrocitario del cordón umbilical.

La constitución aminoácida del armazón proteico del estroma de los eritrocitos del cordón umbilical no difiere cuantitativa ni cualitativamente de la del armazón proteico del estroma de los eritrocitos del adulto.

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Eingegangen den 13. Nov. 1956

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Acta Pædiatrica **46**: 265—285. May 1957

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The Gaseous Metabolism of the Newborn Infant

by K. W. CROSS, J. P. M. TIZARD and D. A. H. TRYTHALL[1]

This paper gives an account of a combined study of pulmonary ventilation and gaseous metabolism in new-born infants. Such a study applied to adults is, of course, a standard and an invaluable procedure, but in the infant only one or other aspect has generally been investigated at one time. (See Cross, 1949, for Pulmonary Ventilation, and Karlberg, 1952, for Gaseous Metabolism, including an excellent review of the literature.)

In July, 1955, since the completion of the work reported here, Cook *et al.* have published a paper with similar data on 18 infants and much additional data. Our methods are essentially similar, but differ in many important details and our focus of interest has been largely different.

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The method used had to fulfil certain requirements.

(1) The infant had to be studied while asleep, with objective evidence of rest previously stipulated when using the body plethysmograph (Cross, 1949).

(2) Observations had to be made with infants breathing air. Because of the difficulty of maintaining a constant oxygen tension in a closed circuit, an open system was considered desirable.

(3) Carbon dioxide production had to be measured, as well as oxygen consumption. This has frequently been neglected in the new-born baby, but this is unjustifiable, as the food which the infant is receiving is very variable both in quantity and quality in the first few days of life, and the

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Our main reasons for carrying out this study are as follows: firstly to provide objective criteria of rest while the metabolism is being measured by a simultaneous measurement of total ventilation; secondly to try to explain changes in the relationship of total ventilation to maturity, weight, age and so on, and thirdly to try to understand changes in ventilation caused by breathing varying gas mixtures.

The method used had to fulfil certain requirements.

(1) The infant had to be studied while asleep, with objective evidence of rest previously stipulated when using the body plethysmograph (Cross, 1949).

(2) Observations had to be made with infants breathing air. Because of the difficulty of maintaining a constant oxygen tension in a closed circuit, an open system was considered desirable.

(3) Carbon dioxide production had to be measured, as well as oxygen consumption. This has frequently been neglected in the new-born baby, but this is unjustifiable, as the food which the infant is receiving is very variable both in quantity and quality in the first few days of life, and the

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post-absorbtive state (as defined in metabolic studies in adults) will never occur.

(4) Drugs could not be used, for although they could be very useful in obtaining long periods of quiet sleep, separate pharmacological studies would be necessary to evaluate their effects on metabolism and ventilation.

(5) As it was proposed in the future to examine the effect of changing oxygen environment, it was necessary to devise a method by which two tests with different gases could be made during one period of sleep. The period for a single observation had therefore to be short.

In this communication we describe the method adopted in this study, and also the results obtained on 68 examinations of premature and full-term infants while breathing air.

Method

Subjects

The subjects examined were full-term and premature infants in the nurseries of St. Mary's Hospital and Hammersmith Hospital, between January 1954 and April 1955. The definition of prematurity has been taken to be babies of less than 2.5 kg at birth. Forty-two full-term infants were examined on 47 occasions, and 14 premature infants were examined 21 times. All the infants were in the first 15 days of life, and examinations were only carried out with the mother's permission.

Technique

The infant was placed in the body plethysmograph (Cross, 1949) at differing periods after feeds. When at rest, a mask was placed over the face and outdoor air drawn through it by a suction pump. In order to keep the rate of air flow as slow as possible without allowing the infant to re-breathe its own expired air, this face-mask had to be specially designed (see Fig. 1).

It consisted of a perspex tube 3 cm in diameter, split longitudinally and held lengthwise over the nose and mouth of the sleeping infant by a rubber diaphragm which lay close to or actually touching the face. The rubber diaphragm was cemented to the rim of a hole cut in a 1-inch thick perspex plate. The hole was of the same size and shape as the face-hole in the lid of the plethysmograph. The perspex plate could be temporarily sealed to the lid with a continuous ring of liquid paraffin.

The air collected from this chamber contained all the expired air of the infant diluted by a varying quantity of atmospheric air. As rates of metabolism were obtained by analysing this air, it was necessary to keep the dilution factor as low as possible. On the other hand, normal metabolic and respiratory behaviour cannot be expected if the infant is allowed to re-breathe its own expired air. A flow rate of approximately two litres a minute was found to be a suitable compromise, and two types of test appear to justify this.

(1) A thin polythene tube was introduced into the mask and samples of air collected slowly through it. It was found that with this flow rate there was no increase in carbon dioxide concentration when the end of the tube lay cephalad to the bridge of the nose, but, of course, such a rise occurred when the tube was caudad to the nares.

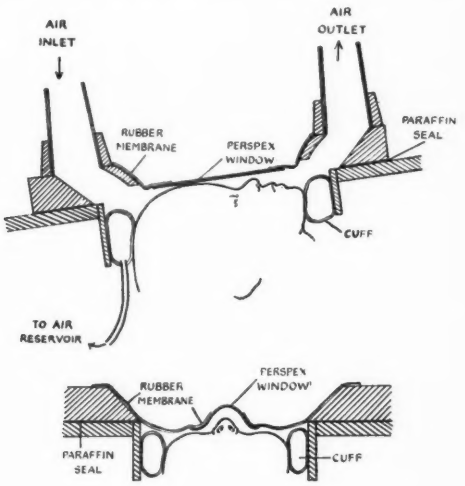

Fig. 1. Diagrammatic (*a*) longitudinal, (*b*) transverse section of the chamber used for collection of expired air from the baby. For the sake of clarity the rubber membrane is shown separated from the face and cuff in the transverse section.

(2) It was found that with this mask and this flow rate there were no increases in minute volume of respiration, as compared with a time when the infant was breathing room air without the mask. (It should be remembered that it has been shown that the infant is highly sensitive to a rise in carbon dioxide concentration in the inspired air, $\frac{1}{2}$ % carbon dioxide showing a significant effect (Cross, Hooper & Oppe, 1953)).

These tests were carried out in full-term infants.

The degree to which the expired air was diluted by atmospheric air in the flask differed for premature and full-term infants. For prematures, the dilution factor varied between 4.2 and 9.7 with a mean of 7.13, while for full-terms, it varied between 3.4 and 6.5 with a mean of 4.53.

When the expired air was to be collected it was drawn into 20 litre aspirator bottles, which were filled with a solution containing glycerine and saturated sodium chloride solutions in equal parts. (Gas analyses showed that this solution did not cause any perceptible change in the composition of a mixture of expired air stored over 12 hours, although in practice analysis was carried out soon after the experiment.) This rather cumbersome method of gas collection was found necessary, as the standard laboratory Douglas Bag and plastic bags designed for gas collections were thoroughly tested and found to leak carbon dioxide differentially. Air or other gas mixture was drawn into these bottles by pumping out the solution at a constant rate, and a period of collection could be started at any time after the mask had been placed over the face (Fig. 2). During both the period of preparation and the period of collection of the expired air, a continuous trace of the infant's breathing was available. This gave objective evidence of rest, and moreover, by measuring the minute volume, one could estimate the percentage of respiratory gases in the expired air.

Gas analysis was carried out in duplicate in two 21 ml Haldane Gas Analysis Apparatuses. Duplicate analyses for carbon dioxide were identical to 0.00 % in 38 of the 68 examinations, and for oxygen in 42. A discrepancy as large as 0.03 % between duplicates for either oxygen or carbon dioxide was found on 6 of the 136 occasions.

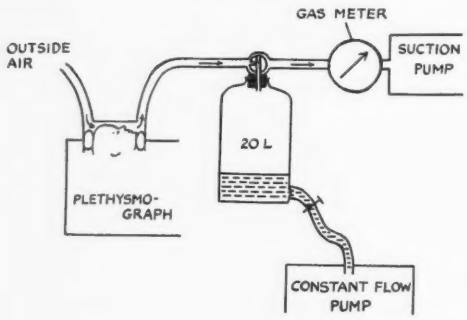

Fig. 2. Diagram of system for collection and storage of air which has passed over the infant's face.

The remaining errors lay between these extremes, and the effect of these errors on the overall accuracy of the results will be assessed later (see Appendix I).

Gas volumes were measured from a calibrated millimetre scale etched on the sides of the aspirator bottles; these were mounted on firm stands which could be accurately levelled. The calibration was carried out by reading the fluid levels with a magnifying glass after successive aliquots had been emptied into litre or 100 ml measuring flasks. Calibrations were carried out over the working range of the aspirators, that is, where the walls were parallel, giving volumes between 6 and 18 litres. It was found that volumes could be read to within 15 ml. Thermometers in the aspirators gave the temperature to $\frac{1}{2}$°C, and the gases collected over this fluid were assumed at all times to be fully saturated with water vapour.

Measurement of minute volume

The precise error involved in the measurement of the minute volume of the sleeping infant is more difficult to estimate, but it is probably about 5 % (Drorbaugh & Fenn, 1955). It is almost certainly the largest single error here, but one which does not affect our metabolic results.

Appendix I gives a mathematical evaluation of the overall errors involved.

Results and Discussion

Tables 1 and 2 summarise the results of the investigations.

This investigation has led to the collection of a great deal of data, and it is probable that there are a great many correlations which we have not tested or appreciated. In studying the results it has been found that for certain characteristics—e.g. minute volume related to weight (see Fig. 3)—the premature and full-term infants behave as though belonging to one fairly homogeneous population, and for this reason one regression line has been calculated for the entire 68 observations. On the other hand, another pair of characteristics—e.g. minute volume related to per cent carbon dioxide in expired air (see Fig. 8A)—show no overall correlation for the two groups combined, but give significant correlations when each group is

TABLE 1

Data obtained from 42 full-term infants examined on 47 occasions.

Subject's number	Age (days)	Sex	Weight in kg		Minute vol. B.T.P.S. ml.	Expired air		R.Q.	ml O_2 consumed at NTP			ml CO_2 produced at NTP		K. Cals.		
			at birth	at exam.		% O_2	% CO_2		/minute	/kg/hour	/kg birthwt./hr.	/minute	/kg/hour	/24 hours	/kg/24 hours	/kg birthwt. 24 hours
1	7.13	M	3.06	3.01	352	13.96	5.62	.76	21.47	428	421	16.40	327	147	48.7	
2	4.13	M	3.37	3.06	609	15.88	3.69	.68	27.90	547	497	19.07	374	187	61.2	
3	4.00	M	3.26	3.12	459	14.14	5.18	.71	25.74	495	474	18.36	353	174	55.7	
	8.00			3.20	549	15.68	4.60	.84	24.00	450	442	20.21	379	168	52.6	
4	7.50	M	2.86	2.72	439	15.13	5.00	.83	21.81	481	457	18.04	398	152	55.8	
5	1.88	F	3.63	3.46	415	15.12	4.37	.70	21.39	371	354	14.99	260	144	41.5	39.6
6	11.13	M	3.35	3.18	383	14.62	5.38	.81	20.72	391	371	16.85	318	143	45.1	
7	2.65	M	3.29	3.06	446	15.54	4.31	.75	21.11	414	385	15.91	312	144	47.0	43.7
8	8.50	M	3.01	3.01	564	16.60	4.03	.91	20.72	413	413	18.81	375	147	49.0	
9	4.00	M	2.50	2.41	393	14.50	5.20	.76	21.93	546	533	16.71	416	150	62.2	
10	4.88	F	3.32	3.06	684	17.46	3.10	.86	20.30	398	367	17.49	343	143	46.6	
11	1.65	M	3.09	2.92	539	16.30	3.87	.79	21.56	443	419	17.13	352	149	50.9	48.1
12	1.75	F	3 57	3 40	426	15.28	4.80	.81	20.74	366	349	16.77	296	144	42.4	40.4
13	8.65	F	2.95	2.92	483	15.63	5.11	.95	21.32	438	434	20.15	414	153	52.4	
14	6.00	F	3.35	3.26	478	16.08	4.05	.79	19.34	356	346	15.32	282	133	40.8	
15	8.65	M	3.57	3.37	506	15.52	3.98	.79	23.81	424	400	18.93	337	164	48.8	
16	1.38	F	3.97	3.83	679	16.82	3.29	.75	24.38	382	369	18.45	289	166	43.4	41.9
17	2.38	M	2.90	2.72	504	16.59	3.43	.74	19.04	420	394	14.14	312	129	47.5	44.6
18	0.50	F	3.80	3.80	515	15.78	3.97	.72	23.31	368	368	16.85	266	158	41.5	41.5
19	2.50	F	3 35	3.03	497	15.95	4.13	.79	21.41	424	383	16.87	334	147	48.6	44.0
20	8.00	F	3.01	2.86	404	15.08	4.49	.72	20.69	434	412	14.87	312	140	49.0	
21	5.88	F	3.40	3.32	427	14.99	4.93	.79	21.97	397	388	17.37	314	151	45.6	
22	6.75	F	3.69	3.60	513	15.12	4.88	.80	25.74	429	419	20.64	344	178	49.4	
23	3.25	M	3.18	2.90	516	16.36	3.52	.72	20.54	425	388	14.74	305	139	47.8	
24	0.19	M	3.97	3.91	467	15.30	4.96	.85	22.42	344	339	19.03	292	157	40.1	39.5
25	1.58	M	4.00	3.83	434	14.70	4.91	.74	23.81	373	357	17.68	277	162	42.4	40.6
26	8.00	F	3.43	3.23	457	14.91	5.16	.82	24.87	442	416	19.49	362	165	51.1	
27	0.19	M	3.80	3.80	508	16.52	4.24	.94	18.81	297	297	17.73	280	151	39.8	39.8
	0.36			3.80	511	15.62	4.47	.80	23.43	370	370	18.81	297	162	42.6	42.6
28	2.38	M	2.67	2.64	364	15.97	4.03	.77	15.66	356	352	12.01	273	107	40.6	40.1
29	0.42	M	3.52	3.49	517	15.57	4.13	.72	24.37	419	415	17.57	302	165	47.3	46.9
	1.46			3.37	519	15.61	4.03	.71	24.32	433	415	17.19	306	164	48.7	46.6
	1.63			3.46	555	15.76	4.44	.82	24.39	423	416	20.07	348	170	49.0	
30	7.50	M	3.06	3.09	541	15.98	4.63	.91	22.66	440	444	20.70	402	161	52.1	
31	7.13	M	3.20	3.01	528	15.95	4.08	.77	23.38	466	438	17.91	357	160	53.2	
32	4.00	M	2.72	2.55	456	15.28	4.24	.70	22.65	533	500	15.81	372	152	59.8	

Table 1 (continued)

Subject's number	Age (days)	Sex	Weight in kg		Minute vol. B.T.P.S. ml	Expired air		R.Q.	ml O_2 consumed at NTP			ml CO_2 produced at NTP		K. Cals.		
			at birth	at exam.		% O_2	% CO_2		/minute	/kg/hour	/kg birthwt./hr.	/minute	/kg/hour	/24 hours	/kg/24 hours	/kg birthwt. /24 hours
33	1.88	M	3.57	3.37	480	16.07	3.47	.66	20.50	365	345	13.54	241	137	40.6	38.3
34	4.88	F	3.32	3.29	627	16.40	3.71	.77	24.57	448	444	18.97	346	168	51.2	
35	4.88	M	4.03	3.77	507	15.90	4.09	.76	22.62	360	337	17.22	274	154	40.9	
36	1.68	F	2.95	2.81	333	14.16	4.92	.67	19.95	426	406	13.39	286	133	47.5	45.2
37	3.71	F	4.45	4.14	468	14.03	5.59	.76	28.01	406	378	21.39	310	192	46.3	
38	4.00	F	3.74	3.54	375	13.88	5.26	.70	23.19	393	373	16.11	273	156	44.0	
	10.96			3.80	543	15.16	5.02	.84	26.85	424	431	22.48	355	187	49.3	
39	7.00	M	3.40	3.32	633	15.35	5.05	.88	29.99	542	529	26.12	472	210	63.3	
40	7.96	M	3.46	3.37	497	15.25	4.75	.79	24.60	438	427	19.55	348	137	40.6	
41	4.09	F	4.08	3.77	478	15.81	3.83	.70	23.88	380	351	16.65	265	161	42.7	
42	5.50	M	2.95	2.69	329	14.89	5.17	.82	17.04	380	347	13.94	311	118	44.0	

considered separately. We have therefore combined the data when there is an overall relationship, and separated it when two different relationships exist. This rather arbitrary treatment has the advantage of economising in space, but may well on occasion be misleading in its implications.

Table 3 shows an analysis of the babies examined together with the respiratory data.

It will be observed that there is a preponderance of males in both groups of infants, but there was no conscious selection of the subjects in relation to sex. Observations were repeated more often on the premature than upon the full-term infants, because of the comparative shortage of healthy premature babies in the chosen age group.

Apart from sex difference, the other findings in Table 3 are in general agreement with previously published values, but it should be noted that the minute volume of the full-term infants is significantly less than those found by Cross (1949), although not very different from the figures found by Cross, Hooper & Oppé (1953) on a larger series. We cannot explain this discrepancy.

Fig 3 shows the relationship between the weight and the minute volume of respiration in the 68 examinations. The correlation found here does not differ significantly from that previously found, but it is worthy of emphasis here because weight and minute volume are two measurements which are used repeatedly in this study as a basis of reference for other variables.

TABLE 2

Data obtained from 14 premature infants examined on 21 occasions.

Subject's number	Age (days)	Sex	Weight in kg		Minute vol. B.T.P.S. ml	Expired air		R.Q.	ml O_2 consumed at NTP			ml CO_2 produced at NTP		K. Cals.		
			at birth	at exam.		% O_2	% CO_2		/minute	/kg/hour	/kg/birthwt.hr.	/minute	/kg/hour	/24 hours	/kg /24 hours	/kg birthwt. /24 hours
1	1.19	F	2.19	2.04	335	16.80	3.10	0.70	11.97	352	328	8.43	248	82	40.0	37.3
	5.29			1.96	364	16.90	3.25	0.76	12.51	383	343	9.51	291	86	43.7	
2	1.63	F	2.04	1 96	367	16.71	2.99	0.65	13.72	420	404	8.95	274	91	46.6	44.8
	2.65			2.04	325	15.79	3.63	0.65	14.59	429	429	9.52	280	97	47.5	47.5
3	5.58	M	1.93	1.79	251	16.07	3.69	0.71	10.71	359	333	7.61	255	72	40.4	
4	7.67	M	1.93	1.80	245	15.65	4.06	0.72	11.28	376	351	8.10	270	76	42.2	
5	2.83	M	1.70	1.61	375	17.60	2.21	0.60	11.00	410	388	6.60	246	72	44.9	42.5
6	12.31	F	1.81	1.64	399	16.08	3.97	0.78	16.59	607	550	12.87	471	114	69.6	
	14.31			1.66	357	17.14	3.59	0.92	11.15	403	370	10.29	372	79	47.8	
7	0.56	M	1.96	1.96	456	18.42	2.25	0.86	10.32	316	316	8.85	271	73	37.0	37.0
8	11.69	M	1.33	1.47	322	15.97	4.54	0.89	13.52	552	610	12.01	490	96	65.0	
9	2.79	F	2.14	2.06	263	14.51	4.72	0.68	14.83	432	416	10.09	294	99	48.2	46.4
10	5.27	M	1.86	1.81	336	17.11	3.39	0.85	11.16	370	361	9.47	314	78	43.0	
	7.29			1.83	374	16.84	3.58	0.84	13.30	436	430	11.19	367	93	50.6	
	12.33			1.93	334	16.19	3.66	0.72	13.19	410	427	9.52	296	89	46.3	
11	10.13	M	2.10	2.00	427	16.58	4.04	0.90	15.93	478	455	14.40	432	113	56.6	
12	4.01	F	2.02	1.87	277	15.83	3.86	0.70	12.65	406	376	8.91	286	85	45.6	
	13.00			1.97	413	17.22	3.47	0.91	12.74	388	378	11.59	353	90	45.8	
13	7.04	M	1.86	1.81	343	16.39	4.03	0.85	13.30	441	429	11.34	376	93	51.6	
	9.10			1.91	280	16.46	4.31	0.94	10.54	331	340	9.93	312	76	39.6	
14	5.65	F	2.18	2.15	378	15.49	4.93	0.88	17.45	487	480	15.27	426	123	57.3	

Calorie value of the oxygen consumed

Karlberg (1952) discusses at some length the calorific value of a litre of oxygen consumed by a baby (pp. 66–78). We have used here the tables based on Zuntz & Schumberg (1901) to give the calories produced per litre of oxygen consumed at differing Respiratory Quotients, but it will be observed from our results that in 7 of 68 observations the Respiratory Quotient is below 0.7. In a steady state these values are never found in the adult human subject, and it was difficult to decide what calorific values to ascribe to an aliquot of oxygen consumed in these circumstances. We have, in fact, extrapolated from the tables provided and assumed the calorific value to be proportionately lowered in a baby with a Respiratory Quotient less than 0.7. While this is almost certainly wrong there are reasons

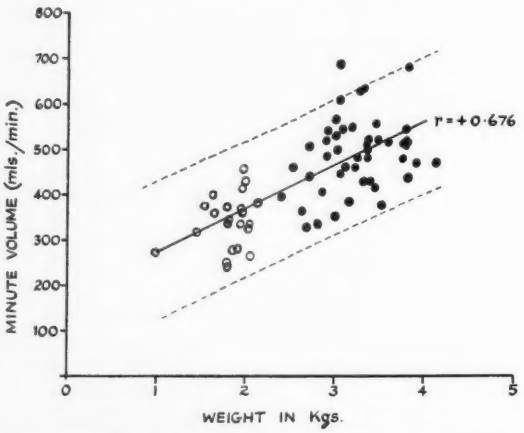

Fig. 3. Relation between weight and minute volume of respiration of premature and full-term infants. The regression line of minute volume on fixed weight is shown, with the 95 % confidence limits of the line. The formula for the line is:—

Minute Volume in ml = 92.04 × wt. (in kg) + 182.45.

Here, as in all subsequent graphs, premature infants are shown as open circles and full-term infants as closed circles.

TABLE 3

Analysis of the subjects and the results obtained.

	Full-term infants		Premature infants	
No. of observations	47		21	
No. of infants				
Male	25		8	
Female	17		6	
Total	42		14	
Age range (days)	*0.19–11.13*		*0.56–14.31*	
Mean wt. in kg and S.D.	3.26	0.404	1.87	0.183
Mean Minute Vol. (ml) and S.D.	487.4	81.67	343.9	57.46
Mean Respiratory Rate and S.D.	30.99	7.13	32.40	10.68
Mean Tidal Air and S.D.	16.50	3.53	11.42	3.33
Mean O_2 consumption/kg/hr. & S.D.	419.11	53.45	418.38	69.18
Mean CO_2 production/kg/hr. & S.D.	326.33	48.15	330.14	74.24

for supposing that in the early days of life *all* babies may to some extent have Respiratory Quotients which are falsely low and by this procedure we hope to have ascribed energy productions to the different babies which bear a reasonable proportionality to one another. (The possible significance of the low Respiratory Quotients is discussed later in the paper.)

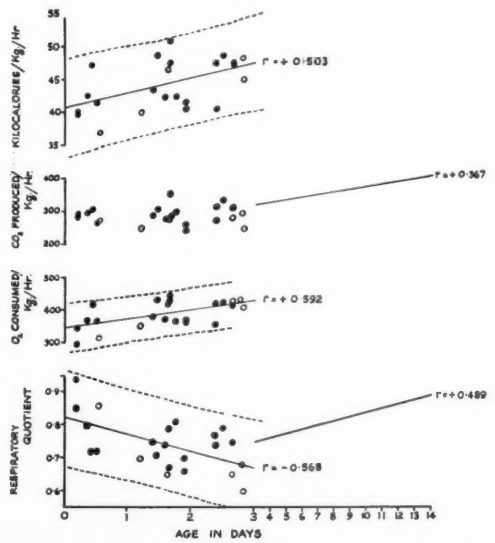

Fig. 4. Changes of calorie production, CO_2 production, O_2 consumption/kg body wt./hr. with fixed age. Also changes of R.Q. with age. The details of the scatter of estimated readings of less than 3 days of age are given on an extended linear scale. The regression lines are plotted for CO_2 production and R.Q. for fixed age for days 3–15. There is no significant relationship at this age for O_2 consumption or calorie production in relation to age.

Kilocalories/kg/24 hr.	=	2.17 × Age +	40.76	(Age 0– 3 days)
CO_2 prod./kg/24 hr.	=	7.41 × Age +	295.9	(Age 3–15 days)
O_2 consum./kg/24 hr.	=	27.27 × Age +	345.01	(Age 0–3 days)
R.Q.	=	−0.05 × Age +	0.82	(Age 0– 3 days)
R.Q.	=	0.013 × Age +	0.7098	(Age 3–15 days)

Metabolic Results

(1) *Changes with age*

In Fig. 4 there is a comparison between certain variables and the age of the newborn. It has become apparent that there are certain changes which are very marked in the first three days of life, some of which might be predicted and have been noted previously, but others which are surprising and have no obvious explanation.

It is not surprising that the Respiratory Quotient should fall in the first three days of life, as the infant at birth will have a supply of glycogen and glucose which will tend to diminish until feeding is established, and is adequate in calories. We find, as has been found before by Benedict & Talbot and others, that there is a statistically significant fall in the Respiratory Quotient in the first three days of life, and this is followed from the third

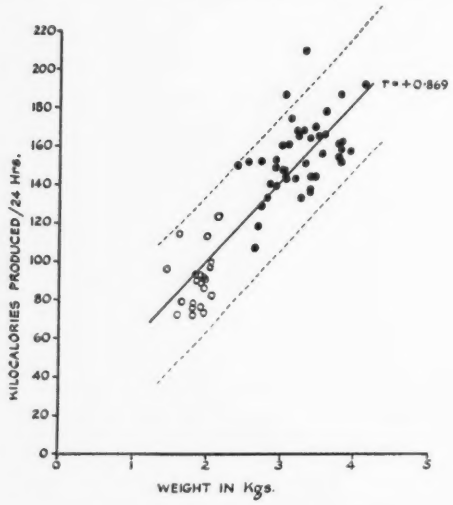

Fig. 5. Relation between the Kilocalorie production/24 hr. and the weight of the premature and full-term infants.

Kilocalories prod./24 hr. =
= 41.65 × wt. + 16.72

to the fourteenth day by a significant rise. Judged by available carbohydrate alone, such a change is understandable, but the method by which the initial fall is brought about is somewhat surprising. One finds that in the first three days of life there is a rising oxygen consumption with a rate of carbon dioxide production which remains about constant. This result is even more surprising when one refers to the Kilocalorie production per kilo body weight, for one finds that this is rising during these first three days. This increasing energy production might perhaps be a false finding, for of course, the body weight falls heavily in these first three days, and the results were therefore recalculated on the basis of Kilocalories produced and ml of oxygen consumed per kilogram of birth weight per hour. Here we find that the rise in calorie production is no longer significant, but in view of the difficulty already described in attributing calorie values to the oxygen consumed by babies with the lowest Respiratory Quotients, it is perhaps of greater interest that the rise in oxygen consumption is still significant when calculated on the basis of birth weight ($r = 0.475$, $p < 0.05$).

From the third to the fifteenth day the oxygen consumption and calorie production per unit of body weight did not rise, but, as might be inferred from the rising Respiratory Quotient, the production of carbon dioxide increased significantly ($r = 0.367$, $p < 0.02$).

(2) *Changes with weight*

There is a remarkably close correlation between the weight of the infants and the calculated calorie production per 24 hours (Fig. 5). It is interesting

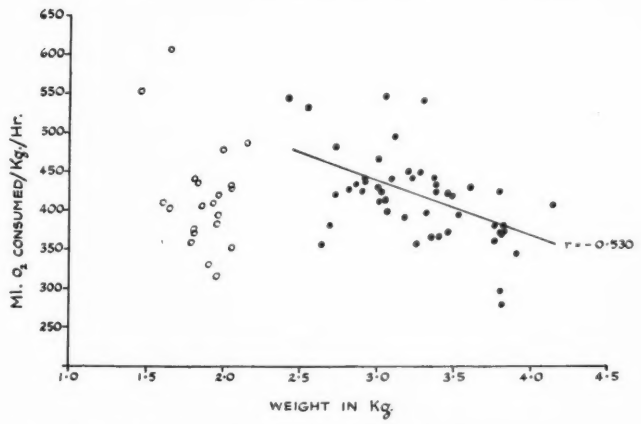

Fig. 6. ml O_2 consumed/kg body wt./hr plotted against weight. Note that the premature infants do not have a higher average oxygen consumption per unit of body weight than the full-term infants. Regression line for full-term infants.

ml O_2 consumed/kg body wt./hr. = $-70.107 \times$ Weight $+ 647.72$

that the calorie production per unit of body weight is about half that of the milk customarily considered sufficient. But these babies were at rest, and it is relevant that in a few instances we noticed a three to fourfold increase in oxygen consumption when the baby cried.

The fact that the consumption of oxygen does not rise significantly with age is presumably due to the small weight gain of individual infants in ten days compared with the weight scatter between infants.

As would be expected, there is a significant positive correlation between weight and both oxygen consumption and carbon dioxide production ($r = 0.870$ and $r = 0.872$ respectively, $p < 0.001$ for both).

(3) *Influence of maturity on metabolism*

The oxygen consumption per kg of body weight per hour varied inversely with the weight of the full-term babies as might be expected on the basis of surface area laws (Fig. 6). That no such significant relationship is found in the premature babies might be due to the fact that their weight range is necessarily small compared with the full term, whereas the individual variations in oxygen consumption are as great.

It is of interest, however, that the mean oxygen consumption per kilogram per hour is the same in both groups (Full-term = 419 ml; Premature =

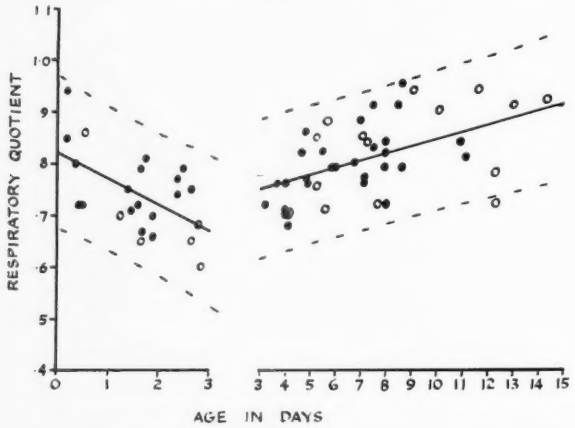

Fig. 7. Relationship between Respiratory Quotient and age of the infants. Regression lines are as given on Fig. 4. Note that the time scale is discontinuous and expanded for the first three days of life.

TABLE 4

Analysis of Respiratory Qoutient with age.

The heading of "Up to 0.7" means R.Q.'s that are less than and include 0.7.

	0–24 hrs.		1–4 days inclusive		5–15 days	
	Up to 0.7	>0.7	Up to 0.7	>0.7	Up to 0.7	>0.7
Full term	0	5	7	20	0	15
Premature	0	1	6	0	0	14

418 ml). On a surface area basis one would expect this figure to be considerably greater for the group of premature infants and that it is not suggests that the general level of metabolic activity is depressed in infants born prematurely.

(4) *Respiratory Quotient*

It will be seen from Table 4 and Fig. 7 that especially in the premature infant Respiratory Quotients tend to fall below 0.7 round about the third day of life.

When the inherent inaccuracies of our methods are taken into account these lowest figures for Respiratory Quotient, like those of Benedict & Talbot and other workers, are significantly less than would be considered possible in the resting state of an adult under any nutritional circumstances.

(See Karlberg, 1952, pp. 74–76, for review on infants' R.Q.'s.) There must be some additional factor operating to reduce the Respiratory Quotient, not necessarily only at the third day of life, but possibly throughout the neonatal period, but only revealed at this time because the infant is then presumably living on its fat, combustion of which proceeds with a lower Respiratory Quotient (0.707) than is the case with carbohydrate and protein.

We have considered the following possibilities to explain the Respiratory Quotients of less than 0.7.

(1) Recovery from hyperventilation (respiratory alkalosis).
(2) Recovery from metabolic acidosis.
(3) Excretion of carbon dioxide in the form of bicarbonate.
(4) Conversion of fat to carbohydrate.
(5) Carbon retention due to rapid growth.
(6) Extrapulmonary gaseous exchange.

Recovery from hyperventilation

We have earlier emphasized that in these experiments we have had objective evidence of respiratory behaviour throughout. In each case the baby was breathing quietly for at least 20 minutes before the beginning of the test period. It is perhaps possible that this period was insufficient to allow recovery of equilibrium of blood gases following a prolonged bout of crying. However, in a series of experiments, to be published elsewhere, there was no tendency for the Respiratory Quotient to rise in successive tests during one period of sleep.

Recovery from metabolic acidosis

It is well established that in both full-term and premature new-born infants there is a degree of metabolic acidosis (premature: Reardon *et al.*, *Pediatrics*, 1950; full-term: Graham *et al.*, *Pediatrics*, 1951). It seems possible that in recovering from this the baby would develop a low Respiratory Quotient, as a result of retaining carbon dioxide. Calculations show, however, that even if the acidosis were extreme and the transition to adult levels very rapid it would hardly reduce the Respiratory Quotient by a significant amount.

Excretion of carbon dioxide in the form of bicarbonate

In the first few days of life the new-born infant passes relatively little urine and it is of acid reaction, so that significant loss of bicarbonate by this route hardly seems likely.

Conversion of fat to carbohydrate

The liver of a new-born baby (mean weight 120 g) is said to contain 1–2.15 g of glycogen/100 g (Camerer, quoted by Feldman) and it is clear that even if the liver glycogen were entirely removed it would not suffice to maintain the total caloric production for more than an hour or two. Moreover, although new-born babies tend to be hypoglycaemic the level of blood glucose is maintained in the first few days of life. Gluconeogenesis must under these circumstances be taking place. McCance & Strangeways have shown that protein katabolism provides less than 4 per cent of energy during the first 48 hours of life, and it is therefore clear that carbohydrates must be being formed largely at the expense of fat. If the conversion of fat to carbohydrate were carried out with complete efficiency, and if the carbohydrate thus formed were entirely metabolised, the resulting Respiratory Quotient would presumably be the same as that for the combustion of fat (0.707). Only if stores of carbohydrate were being increased at the expense of fat, which seems inherently unlikely, would the Respiratory Quotient be lowered below that found with complete combustion of fat. Incomplete combustion of fat would also tend to lower the Respiratory Quotient. On testing the urine of new-born babies we have found consistently positive Rothera's Test for acetone from the second to fourth or fifth days of life, but negative ferric chloride tests for aceto-acetic acid. In any case, the degree of ketosis required to account completely for a fall in Respiratory Quotient from say, 0.7 to 0.6, would be absurdly high.

Carbon retention due to rapid growth

Although carbon dioxide fixation has been regarded as an attribute of the vegetable world it can occur in the animal world (see for example Hendler, 1956). In the presence of the fluid loss that takes place in the first few days of life it is difficult to say if deposition of new tissue takes place. But while growth would seem to be at its lowest at about the third day, this possible explanation of lowered carbon dioxide production does not have the quantitative objections of the other mechanisms considered above.

Extrapulmonary gaseous exchange

It has frequently been suggested that some gaseous exchange is possible across the skin of the new-born baby (see Smith, 1951, p. 57, for discussion and references) and it is known that some absorption of oxygen is possible from the stomach and the bowel (Åkerrén & Fürstenberg, 1950). If oxygen can be absorbed through the skin it seems likely that more carbon dioxide

would be excreted by the same route and this would have the effect of producing a falsely low Respiratory Quotient as measured by respiratory gaseous exchange. Krogh (1904) has shown that in the pigeon the Respiratory Quotient of the skin is consistently above unity, and this observation appears to hold good for other vertebrates. It is interesting that we have found the lowest Respiratory Quotients in premature babies, who have the thinnest skins.

The question of extrapulmonary gaseous exchange needs to be investigated and unless it can be excluded as a significant factor direct calorimetry in the new-born will be necessary.

Of the possibilities we have discussed that of extrapulmonary loss of carbon dioxide seems the most reasonable possible explanation of the low Respiratory Quotients.

Although we cannot be dogmatic about the causes of the low Respiratory Quotients in the new-born infant we have thought it worth while to discuss the matter in some detail, for we have failed to find such a discussion in the literature and we feel that the enumeration of at least some of the possible causes has indicated further lines of investigation.

Time after feed

In all cases, when a baby's metabolism was examined the time since the last feed was noted. We have examined the data to see if a recent feed has any obvious effect on oxygen consumption and Respiratory Quotient. No such relationships have been observed and we presume that the larger effects of age on Respiratory Quotient have overshadowed the minor effects due to the most recent feed.

Respiratory Results

As we have been able to measure both the minute volume of respiration and the minute consumption of oxygen and production of carbon dioxide, it has been possible in each infant to estimate the percentage of oxygen and carbon dioxide in the expired air.

Minute Volume

We find that there is a less close correlation between weight and minute volume ($r = +0.676$), than there is between weight and calorie production ($r = +0.869$). If there were a perfect relationship between energy requirements and minute volume, the gaseous composition of the expired air would remain constant. But, in fact, babies with a higher minute volume

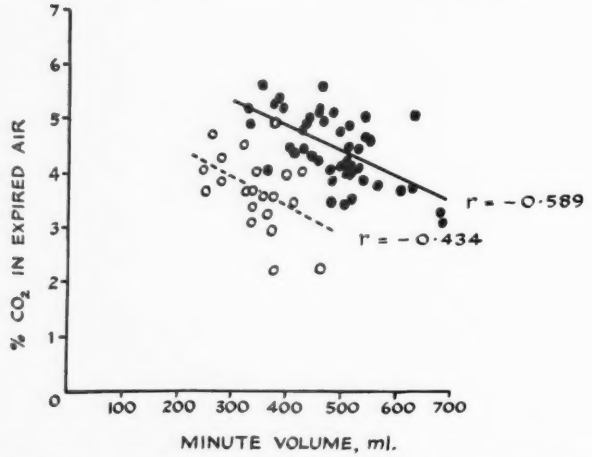

Fig. 8A. % CO_2 in expired air compared with minute volume of respiration.
For full-term infants: % CO_2 in expired air = − 0.0046 × Minute Vol. + 6.73
For premature infants: % CO_2 in expired air = − 0.0052 × Minute Vol. + 5.48

tend to have less carbon dioxide and more oxygen in expired air than those with a low minute volume (see Figs. 8A and 8B) from which we conclude that, as in the adult, minute volume is not solely determined by metabolic requirements. But it is clear that energy requirements do influence minute volume to a large extent as shown by the positive relationship between minute volume and oxygen consumption and carbon dioxide production ($r = +0.741$ and $+0.775$ respectively).

Effect of Maturity on Respiratory Gases

The conclusions just stated apply to premature and full-term infants considered as a whole. It is interesting to note, however, that the premature and full-term infants fall into two more or less distinct populations when the percentage of expired gases is considered in relation to minute volume of respiration. There is a significantly lower mean percentage of oxygen, and higher percentage of carbon dioxide in the expired air of the full-term infant ($O_2 = 15.49\%$, $CO_2 = 4.45\%$) than in that of the premature infant ($O_2 = 16.46\%$, $CO_2 = 3.68\%$) ($p < 0.001$ for each). Differences in composition of the alveolar air in premature and full-term infants would obviously be related to differing arterial blood gas tensions, and these might be caused by several factors, including difficulties in diffusion across the pulmonary membrane, which in the small premature baby, at least, is structurally

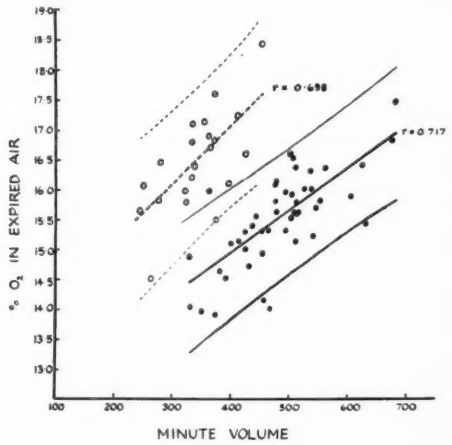

Fig. 8B. % O_2 in expired air compared with minute volume of respiration.

For full-term infants: % O_2 in expired air = 0.0069 × Minute Vol. + 12.128
For premature infants: % O_2 in expired air = 0.0096 × Minute Vol. + 13.168

different. We cannot consider our results in relation to the new-born baby's arterial oxygen tensions because this has never been measured directly. Measurements of arterial carbon dioxide tensions in premature (Reardon *et al.*, 1950) and full-term babies (Graham *et al.*, 1951) show no significant difference in the carbon dioxide tension of the two groups. However, the measurement of arterial carbon dioxide tension in the new-born is not altogether satisfactory, and the very wide scatter needs explanation. For instance, the range of arterial carbon dioxide in premature infants (Reardon *et al.*, 1950) varies between 21 and 58 mm Hg, which would correspond to figures of approximately 3% and 8% alveolar carbon dioxide. But if one accepts that there is no significant difference in the arterial carbon dioxide tension of premature and full-term infants, the difference in carbon dioxide content of their expired air in our groups can only be explained by differences in dead space.

Dead Space

The difference between the mean carbon dioxide in expired air in the full-term and premature babies is 0.77%, and this is highly significant ($p < 0.001$). Assuming that the arterial pCO_2 is approximately the same in both groups, the dead space of the premature baby will be approximately 1.3 times that of the full term and if the arterial pCO_2 of the premature is lower than that of the full term (as found, for instance by Cook *et al.*, 1955) the discrepancy between the relative sizes of their dead space will be even greater. This is contrary to the findings of Cook *et al.*

Acknowledgements

We are indebted to many people for helping us to undertake this work. We had financial support for apparatus and the excellent technical assistance of Miss Jennifer Lowe from the St. Mary's Hospital Research Fund and the Halley Stewart Trust. The subjects examined were in the Maternity Wards of St. Mary's Hospital (Sister K. A. Taylor), Hammersmith Premature Baby Unit (Miss M. M. Smith) and Paddington General Hospital (Sister Shields). We would like to acknowledge the help of these ladies and also to thank the Management Committees of these hospitals for permission to carry out this work.

Summary

1. A method is described for measuring the oxygen consumed and the carbon dioxide produced over short periods by new-born babies with simultaneous measurement of their minute volumes of respiration.

2. Measurements were made in 47 full-term babies and 21 premature babies.

3. In 23 examinations in the first three days of life, the oxygen consumption per kilogram of body weight (and per kilogram of birth weight) was shown to rise significantly. During this period the Respiratory Quotient fell. In 45 examinations from the fourth to fourteenth day the carbon dioxide production per kilogram of body weight and the Respiratory Quotient rose significantly. On or about the third day of life, the Respiratory Quotient was at or below 0.7 in 43 % of examinations, but in none on the first day or after the fifth day. The possible reasons for this low Respiratory Quotient are discussed.

In spite of a presumably greater surface area per unit of body weight in the premature infant the mean oxygen consumption per kilogram of body weight was about the same as in the full term.

4. There is a closer correlation between the minute volume of respiration and metabolism than there is between minute volume and weight. The premature baby has a significantly higher percentage of oxygen and lower percentage of carbon dioxide in the expired air than the full-term baby.

It seems that the relative dead space in premature infants is greater than in full-term infants.

Métabolisme gazeux du nouveau-né.

On décrit une méthode de mensuration de l'oxygène consommé et de l'anhydride carbonique produit pendant de courtes périodes, chez les nouveau-nés, simultanément avec la mensuration de leur volume de respiration le plus réduit. Des mensurations ont été effectuées en 47 cas de bébés nés à terme et 21 prématurés. Dans les 23 cas examinés aux trois premiers jours de la vie, on a pu constater que la consommation d'oxygène par kilogramme de poids corporel (et par kilogramme de poids à la naissance), s'élevait de façon significative. Pendant cette période, le quotient de la respiration tombait. Dans 45 cas examinés depuis le quatrième jour jusqu'au quatorzième, la production d'anhydride carbonique par kilogramme de poids corporel et le quotient de la respiration s'élevaient significativement. Le troisième, ou autour du troisième jour de la vie, le quotient de la respiration marquait, ou se montrait au-dessous de, 0,7 dans 45 % de cas examinés, mais en aucun d'eux dès le premier jour ou après le cinquième jour. Les raisons possibles de ce bas quotient de la respiration, sont développées. Malgré une

extension superficielle présumée plus considérable par unité de poids corporel chez les prématurés, la consommation moyenne d'oxygène par kilogramme de poids corporel a été approximativement semblable à celle des enfants nés à terme. Il existe une plus étroite corrélation entre le volume plus réduit de la respiration et le métabolisme, qu'il n'en existe entre le volume plus réduit et le poids. Le bébé prématuré a besoin d'un pourcentage significativement plus élevé d'oxygène et d'un pourcentage inférieur d'anhydride carbonique dans l'air expulsé, que le bébé né à terme. Il semblerait que l'espace mort relatif chez les enfants nés prématurément soit plus grand que chez ceux nés à terme.

Der Gasstoffwechsel des Neugeborenen.

Eine Methode zum Messen des Sauerstoffverbrauches und der Kohlensäureproduktion innerhalb kurzer Zeitabschnitte bei neugeborenen Kindern, mit gleichzeitiger Bestimmung des Minutenvolumens der Respiration, ist beschrieben. Messungen wurden an 47 vollzeitig und 21 frühgeborenen Kindern vorgenommen. In 23 in den ersten 3 Lebenstagen durchgeführten Untersuchungen zeigte es sich, dass der Sauerstoffverbrauch per kg des Körpergewichts (und per kg des Geburtsgewichts) bedeutsam zunahm. In diesem Zeitabschnitt fiel der respiratorische Quotient herab. In 45 zwischen dem vierten und vierzehnten Tag vorgenommenen Versuchen ergab es sich, dass die Kohlensäureproduktion per kg des Körpergewichts und der respiratorische Quotient bedeutend ansteigen. Am dritten oder um den dritten Lebenstag herum betrug der respiratorische Quotient in 45 % der Versuche 0,7 oder etwas weniger, was niemals am ersten oder nach dem fünften Lebenstag der Fall war. Die für diesen niedrigen respiratorischen Quotienten möglichen Gründe werden erörtert. Trotz der wahrscheinlich grösseren Körperoberfläche im Verhältnis zur Einheit des Körpergewichts bei dem frühgeborenen Kind war der durchschnittliche Sauerstoffverbrauch per kg des Körpergewichts etwa gleich gross wie bei dem vollzeitigen Neugeborenen. Es besteht eine innigere Wechselbeziehung zwischen dem Minutenvolumen der Atmung und dem Stoffwechsel, als zwischen dem Minutenvolumen und Körpergewicht. Das frühgeborene Kind hat einen bedeutend höheren Prozentsatz Sauerstoff und niedrigeren Prozentsatz Kohlensäure in der ausgeatmeten Luft als das vollzeitig geborene Kind. Es scheint, dass der relative tote Raum bei dem frühreifen Kind grösser ist als bei dem vollreifen.

Metabolismo gaseoso del recién nacido.

Descríbese un método para medir el oxígeno consumido y el anhídrido carbónico producido durante cortos períodos en los recién nacidos, simultáneamente con la medición de su volumen respiratorio más reducido. Efectuáronse mediciones en 47 casos de bebés nacidos a término y 21 prematuros. En 23 casos examinados en los tres primeros días de la vida, el consumo de oxígeno por kilógramo de peso corporal (y por kilógramo de peso al nacer), comprobóse ascendía significativamente. Durante este período cayó el cociente respiratorio. En 45 casos examinados desde el cuarto día hasta el décimocuarto, la producción de anhídrido carbónico pro kilógramo de peso corporal y el cociente respiratorio ascendieron significativamente. El tercer, o alrededor del tercer día de la vida, el cociente respiratorio acusaba, o estaba debajo de, 0,7 en un 45 % de los casos examinados, pero en ninguno de ellos desde el primer día o después del quinto día. Discútense las razones posibles de este bajo cociente respiratorio. A pesar de una presunta extensión superficial más considerable por unidad de

peso corporal en los prematoros, el consumo medio de oxígeno por kilógramo de peso corporal fué aproximadamente igual al de los nacidos a término. Existe una más íntima correlación entre el volumen respiratorio más reducido y el metabolismo, que la hay entre el volumen más reducido y el peso. El bebé prematuro necesita un porcentage significativamente más elevado de oxígeno y porcentage inferior de anhídrido carbónico en el aire expulsado, que el bebé nacido a término. Parece como si el espacio muerto relativo en los niños prematuros fuera mayor que en los nacidos a término.

Appendix I

Analysis of certain errors

A review of the errors involved is included under "Methods".

(*a*) *Gas analysis*

The following analysis of the possible effect of errors in gas analysis was carried out.

The percentage difference between each of a pair of duplicate observations and their mean was determined and the standard deviation of this difference calculated. We have then taken the 99 % confidence limits for individual observations. The results are as follows: for premature babies, $CO_2 \pm 1.77$ %, $O_2 \pm 0.04$ %; for full-term babies, $CO_2 \pm 1.15$ %, $O_2 \pm 0.06$ %.

We have then examined the effects on the Respiratory Quotient of a combination of largest errors within the 99 % confidence limits, that is the highest for oxygen and the lowest for carbon dioxide and vice versa on an individual. We have selected babies with low Respiratory Quotients in whom the difference between the oxygen and carbon dioxide observations is most pronounced, e.g. for premature Baby No. 3 the Respiratory Quotient could be 0.707 or 0.705, and for Full-Term Baby No. 29 (2nd test), the Respiratory Quotient could be 0.719 or 0.708.

(*b*) *Gas analysis and estimation of volume*

The effect of maximum errors both in gas analysis and the estimation of volume has been calculated for its effect on oxygen consumption.

For Premature Baby No. 3, the lowest estimation could be 354 ml and the highest, 368 ml, a difference of 4 %. (The possible differences of volume of air inspired are related to errors both in reading and in Haldane analysis, the latter involving the conventional nitrogen correction.)

Although this maximum error in oxygen consumption of 2 % from the mean for this particular observation seems large, it is in fact small in comparison to the difference in oxygen consumption between individual babies, which is as high as 83 %.

Appendix II

The % Oxygen and Carbon Dioxide were calculated from the following formulae:

$$\%\ CO_2 \text{ in expired air} = \frac{VF}{VM}\ (\%\ CO_2F - \%\ CO_2At) + \%\ CO_2At)$$

$$\%\ O_2 \text{ in expired air} = \frac{VF}{VM}\ (\%\ O_2F - \%\ O_2At) + \%\ O_2At)$$

VF = Volume of gas collected in aspirator bottle (flask) per minute, dry and at N.T.P.

VM = Minute volume of respiration of infant, dry and at N.T.P.

% CO_2F = % CO_2 found in aspirator
% CO_2At = % CO_2 in atmosphere (taken as 0.03 %)
% O_2F = % O_2 found in aspirator
% O_2At = % O_2 in atmosphere (taken as 20.93 %)

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Received Nov. 16, 1956

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Acta Pædiatrica **46**: 286—293. May 1957

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Protein Metabolism in Chronic Severe Malnutrition (Kwashiorkor)

2. Influence of Aminoacid Supplements on the Absorption and Retention of Nitrogen from a Maize and Beans Diet.

by F. GÓMEZ, R. RAMOS-GALVÁN, J. CRAVIOTO, S. FRENK, CARMEN DE LA PEÑA, MARÍA ELENA MORENO and MARÍA ELENA VILLA

Several authors have reported on the beneficial influence of aminoacid supplements on the growth of experimental subjects. Osborne & Mendel (16) obtained either no growth, or a low rate of growth in rats fed wheat gliadin. On increasing the amounts of lysine in the diet, they were able to induce greater growth rates. Albanese (1) found that wheat gluten did not support normal growth in infants, but the addition of lysine in sufficient amounts to double the normal amount present in the diet, induced a normal growth rate.

Goettsch (8) fed rats with a typical Puerto Rican diet of rice and beans, and found that the animals were smaller in size. The stunting effect of the rice and beans diet early in life could not be fully overcome by changing the animals to a good diet later during their growing period. Improvement of polished rice by supplementation with aminoacids has been reported by Pecora & Handley (17), Arulanantham (3), Deshpande, Harper, Quiroz-Perez & Elvehjem (6).

Corn meal (*Zea mays* L.) and beans (*Phaseolos vulgaris* L.) constitute the main foodstuffs eaten by malnourished people not only in Mexico, Central America and South America, but also in Africa and several parts of Europe. Children with chronic severe malnutrition show very variable absorption and retention of the nitrogen from this diet and there is a poor correlation between nitrogen intake and nitrogen absorption or retention (9).

Since good quality protein foodstuffs are practically impossible to be obtained by malnourished children, and since it has been reported that lysine can increase the weight gain in malnourished infants, it was thought

important to study the effect of aminoacid supplements on the absorption and retention of nitrogen from the typical corn meal and beans diet.

The present report deals on the influence of lysine and tryptophane supplements.

Methods

Four preschool-age children with the typical clinical and biochemical findings of protein malnutrition (10, 18) were placed on metabolic beds in order to collect feces and urine separately. Carmin was used as marker.

The general characteristics of the children are shown in Table 1.

The basal diet consisted of corn-meal and beans and was prepared as previously reported. Aliquots of food were analyzed each time the diet was prepared. A semi-micro Kjeldahl method was used to determine nitrogen content.

After 3 days on the basal diet the children were placed into collection for four-day periods. Each child was fed 4 times a day. Two of the children received first the basal diet, and then the basal plus the supplement, while the other two received first the basal diet plus supplement and the basal diet alone in a later period. Purified *l*-lysine (Lys) and *l*-tryptophane (Try) were used as supplements. The dose was 400 mg per day for each of the aminoacids, divided into four doses in order to give one-fourth of the daily intake at each meal.

In order to test if the level of intake could influence the action of the supplement, in two cases (O. R. G. and J. C. F.) both calories and nitrogen were increased up to about twice the previous level, during the non-supplemented period. In the other two children (R. Ll. R. and Z. A. E.) the intake was more or less constant.

TABLE 1

Age, weight, height, and theoretical weight for the age of four chronic severely malnourished children.

Child	Age	Height (cm)	Weight (kg)	Theoretical weight for the age (kg)
O. R. G.	3 yr. 11 mo.	82	8.900	16.000
R. Ll.R.	1 yr. 4 mo.	70	6.480	9.800
J. C. F.	4 yr.	98	11.300	16.200
Z. A. E.	1 yr. 10 mo.	72	7.780	11.000

Results

Metabolism data on the four children are given in Table 2.

In order to cancel the difference in nitrogen intake, the ratio:

$$\frac{\text{balance/kg/day}}{\text{intake/kg/day}} \times 100$$

was calculated; the data thus obtained are presented in Table 3.

TABLE 2

Mean daily intake, excretion and balance of nitrogen in severely malnourished children on a corn and beans diet with and without supplements of lysine and tryptophane.

Child	Supplement	Calorie intake (cal)	Nitrogen intake (g)	Nitrogen urinary (g)	Excretion		Nitrogen balance (g)
					fecal (g)	total (g)	
O. R. G.	Lys + Try	500	4.811	0.281	2.490	2.771	+ 2.040
	None	996	5.340	0.452	5.040	5.492	− 0.153
R. Ll. R.	None	500	3.263	0.464	1.921	2.385	+ 0.878
	Lys + Try	628	4.566	0.666	1.025	1.691	+ 2.875
J. C. F.	Lys + Try	485	5.455	0.252	2.533	2.785	+ 2.670
	None	1162	8.501	0.929	4.479	5.408	+ 3.093
Z. A. E.	None	486	5.252	1.033	1.967	3.000	+ 2.252
	Lys + Try	451	8.335	1.484	1.759	3.243	+ 5.092

TABLE 3

Nitrogen absorption and retention as per cent of nitrogen intake in severely malnourished children on a diet of corn and beans with and without supplement of lysine and tryptophane.

Children	Per cent of intake absorbed		Per cent of intake retained	
	Without suppl.	With suppl.	Without suppl.	With suppl.
O. R. G.	6	48	− 2.79	+ 42
R. Ll. R.	41	78	27	63
J. C. F.	48	54	36	49
Á. A. E.	63	79	43	61

TABLE 4

Essential aminoacid content mg/100 g fresh food-stuff (microbiological methods).

Food-stuff	Protein g %	Tryptophane	Valine	Threonine	Methionine	Lysine	Histidine	Leucine	Isoleucine	Phenylalanine	Arginine
Corn-meal . . .	8.48	57	537	366	201	239	219	1545	744	588	378
Beans	16.70	230	1295	1063	162	1341	549	2232	1882	1303	883
Milk	3.00	30	142	97	37	192	75	232	127	90	67

TABLE 5

Mean daily intake of essential amino acids.

(Protein intake 36.71 g. Body wt. 10 kg)

Whole milk = 1224 ml.
Beans pure = 360 g = 98.3 g raw beans.
Corn meal = 240 g.

	Beans + corn	Milk	Requirements (E. L. Holt, Jr.)
	(g.)	(g.)	(g.)
Tryptophane	0.36	0.367	0.30
Valine	2.55	1.74	
Threonine	1.91	1.20	0.60
Methionine	0.64	0.46	0.65
Lysine	1.89	2.35	0.96
Histidine	1.06	0.92	
Leucine	5.87	2.85	
Isoleucine	3.63	1.56	0.90
Phenylalanine	2.69	1.10	0.90
Arginine	1.77	0.83	

Figs. 1 and 2 show, respectively, cumulative absorption and cumulative balance expressed as per cent of nitrogen intake.

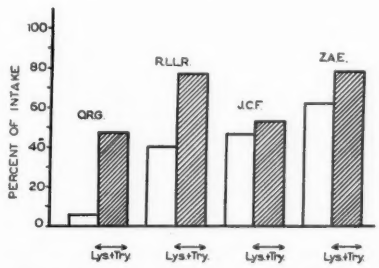

Fig. 1. *Influence of aminoacid supplements on the absorption of nitrogen from a corn-meal and beans diet.*

Cumulative apparent nitrogen absorption (apparent absorption means nitrogen intake minus total fecal nitrogen) of chronic severely malnourished children fed a corn and beans diet with and without lysine and tryptophane supplements. (Values as per cent of intake.)

Discussion

One of the basic purposes of dietary proteins is to provide the organism with a pattern of aminoacids suitable for the synthesis of tissue proteins. Therefore, the analysis of the aminoacid content of the proteins ingested

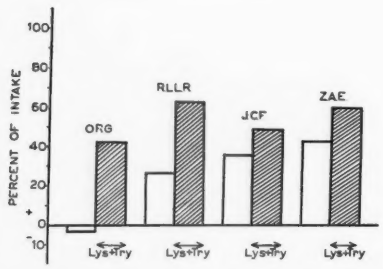

Fig. 2. *Influence of aminoacid supplements on the retention of nitrogen from a corn-meal and beans diet.*

Cumulative balances in severely malnourished children on a corn and beans diet with and without supplements of lysine and tryptophane. (Values as per cent of intake.)

by malnourished children is important since it gives information concerning the potential supply of nitrogen material from the diet.

In Table 4, a comparison is made between the aminoacid content of our two principal sources of proteins, and cow's milk. In general, the diet eaten by our children contains beans and corn-meal in proportions of about 5 to 4. With this in mind Table 5 was constructed, and it shows that with the exception of lysine, the aminoacid content of corn-meal and beans when combined in the mentioned proportions, is equal or greater than the content provided by a similar weight of cow's milk proteins, and above the requirement of essential aminoacids for growth in infancy, as found by Holt jr. *et al.* (13). Nevertheless, when Cravioto *et al.* (5) gave this mixture to rats, as the only source of protein, the weight-gain per gram of protein consumed was of only 0.93 ± 0.37 against a gain of 1.84 ± 0.040 when 22 per cent of the total protein was substituted by milk proteins. These results are in agreement with the biological value of the diet calculated by Mitchell and Block's formula.

In another report it was shown that nitrogen derived from this diet was as a rule poorly absorbed and retained by malnourished children although the absolute figures were variable from child to child. These findings are examples of the fact that for the better utilization of proteins not only the content but the relative proportions of their aminoacids must follow certain patterns, which are as yet not completely known.

From the data of the present report, it seems that apparent absorption and retention are increased by the addition of the supplement.

The analysis of the excretion data shows that the change in urinary nitrogen, although slight, was in one instance greater after feeding the supplement. On the contrary the apparent fecal nitrogen taken as percent of

nitrogen intake, always was much higher when no supplement was given. In other words, the supplement increased the apparent absorption of a diet whose aminoacid pattern, modified by the supplement itself, was of better biological value than the non supplemented diet, and by doing so made possible a greater nitrogen retention.

Taking into consideration the animal experiments together with the aminoacid composition of the diet, the finding of increased nitrogen retention is not surprising.

If one considers that protein absorption is an active process and not merely a diffusion of aminoacids through the intestinal wall, one has to conclude that lysine and tryptophane changed that process in some way. Preliminary experiments in our laboratory seem to disclose that *in vitro* proteolytic hydrolysis of corn-meal is decreased when lysine or tryptophane are added to the substrate in presence of an excess of enzymes. Mellander (15) and Geiger (7) have reported that protein of very similar aminoacid composition are of different nutritional value, and the nutritional value could be inversely correlated with the rate of hydrolysis both *in vivo* and *in vitro*. Therefore, it seems that besides helping to make a more physiological pattern, the supplements of lysine and tryptophane, by lowering the rate of hydrolysis, improved first the absorption and then the retention.

Recently Albanese, Higgons, Hyde & Orto (2) have reported that some children fed on milk formulas with high vitamin and mineral content, improved their nutritional condition when the feedings were supplemented with lysine. The authors state that nitrogen balances were markedly improved by the supplement in 5 out of 15 children. Unfortunately the metabolism data are not given in the report, so it is not possible to decide whether the apparent absorption was modified or not by the supplement. Experiments attempting to clear this point are now under way in our laboratory.

In spite of the data presented, and the fact that some aminoacids such as lysine and methionine are produced in industrial amounts, no wholesale enrichment of corn and beans is as yet to be recommended. The reports of Pecora & Handley (17) who, among others, have shown that increase of lysine to twice its original amount in the diet retarded the growth of rats, and the numerous papers dealing with the production of aminoacid imbalances when certain limiting aminoacids are given as supplements (4, 11, 12, 14, 19) point out the need of continued studies of this type, trying to assess the role of supplements both in normal and in malnourished subjects, before attempting to use these incomplete evidences in the treatment or prevention of malnutrition.

We would like to thank Mead Johnson and Co. of Evansville, Ind., U.S.A., for a grant which enabled this work to be carried out.

Summary

Nitrogen balances were done on children affected with chronic severe malnutrition while on a diet of corn-meal and beans with and without lysine and tryptophane supplements.

Calculated as per cent of intake both absorption and retention of nitrogen were greater when the supplement was added to the basal diet.

Du métabolisme protéique dans la sous-alimentation chronique grave (Kwashiorkor).

2. *Influence des suppléments amino-acides sur l'absorption et la rétention d'azotes dans le régime diététique au maïs et aux légumineuses.*

Chez des enfants souffrant de sous-alimentation chronique grave, des balances ont été établies pendant un régime diététique de farine de maïs et des légumineuses, avec et sans suppléments de lysine et de tryptophane. Calculées en pourcentages de matière ingérée, l'absorption aussi bien que la rétention d'azotes ont été plus grandes lorsque le suppléement était ajouté au régime fondamental.

Eiweißstoffwechsel in schwerer chronischer Unterernährung (Kwashiorkor).

2. *Einfluss ergänzender Aminosäuren auf die Absorption und Retention von Stickstoff bei einer Mais- und Bohnendiät.*

Stickstoffbilanzuntersuchungen wurden bei Kindern mit schwerer chronischer Unternährung, die an einer Maismehl- und Bohnendiät mit und ohne Zusatz von Lysin und Tryptophan gehalten waren, durchgeführt. Es zeigte sich, dass sowohl die Absorption als auch die Retention von Stickstoff, ausgedrückt in Prozenten der Einnahme, grösser war, wenn die zugrundeliegende Diät die zusätzlichen Aminosäuren enthielt.

Metabolismo proteico en la desnutrición crónica grave (Kwashiorkor)

2. *Influencia de los suplementos aminoácidos en la absorción y retención nitrogénicas bajo un régimen dietético de maíz y leguminosas.*

Estableciéronse balanzas nitrogénicas de niños afectos de desnutrición crónica grave, mientras quedaban sometidos a un régimen dietético de harina de maíz y leguminosas, con y sin suplementos de lisinas y triptófano. Calculadas en porcentajes de materia ingerida, tanto la absorción como la retención del nitrógeno, fueron mayores al ser añadido el suplemento a la dieta fundamental.

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Received Nov. 19, 1956

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Acta Pædiatrica 46: 294—300. May 1957

From the Pediatric, Psychiatric and First Medical Departments of the University of Gothenburg, Sweden

A Case of the Pituitary Type of Genetic Diabetes Insipidus Simulating the Nephrogenic Type

by ÅKE ELLBORG, HANS FORSSMAN and BENGT HEISTER

Waring, Kajdi and Tappan (1945) reported a number of symptoms in children with a disease first described in 1942 by one of us (H. F.). The syndrome, manifested shortly after birth, is characterized by polyuria and polydipsia, erratic and unexplained fever, persistent constipation and vomiting. In these cases, the disorder in the water metabolism cannot be kept under control with the antidiuretic hormone, whence the name "nephrogenic diabetes insipidus" coined by Williams and Henry (1947).

In 1955 two of us (Å. E. and H. F.) published a paper in this journal describing 8 cases and recapitulating the literature up to that time. Attention was drawn to the danger of the severe dehydration causing the death of some infants and mental retardation in some of the survivors. This last matter was gone into in more detail in another article by one of us (H. F.) published the same year.

After the first of these papers was submitted for publication, articles by Ford-Walker & Rance (1954), Luder & Burnett (1954), Flax & Gersh (1955), Gautier & Prader (1956), Kirman, Black, Wilkinson & Evans (1956) and Carter & Simpkiss (1956) appeared on the same subject.

The reports mentioned so far have only described cases in boys, and every pedigree of reliable size published has shown the presence of a recessive sex-linked gene. West & Kramer (1955), however, described a family with nephrogenic diabetes insipidus in which the hereditary pattern was strongly suggestive of a simple autosomal gene, though there was no definite proof of this as the disease was never seen to pass from father to son. Three of their 6 unequivocal cases were in women. The infantile syndrome was also noted in this family. This report throws a new light on the hitherto puzzling observation of Dancis, Birmingham & Leslie (1948) of the nephrogenic infantile syndrome in a little girl.

As far as we know the combination of dehydration, vomiting, fever and retarded development seen in infants with diabetes insipidus has hitherto

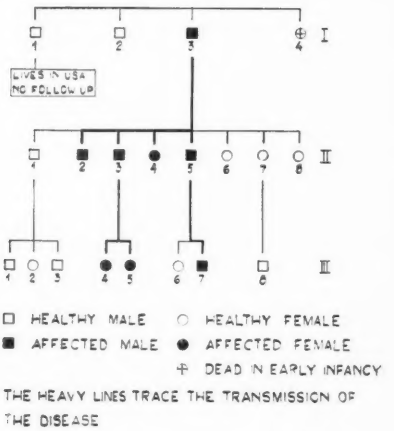

Fig. 1. Number 7 in Generation III = W. O.

only been observed in cases of the nephrogenic form. We shall now describe a case we have just observed, however, of the same syndrome in a boy with the other form of diabetes insipidus, the one sensitive to ADH, which we shall henceforward call the "pituitary" form. The boy, who is now 14 years old, is also mentally deficient.

The pedigree of his family is given in Fig. 1. There we see that it is a question of an autosomal gene which in three places passed from father to son. The boy now to be described is number 7 in generation III.

Case Reports

W. O. was born on July 10, 1942 at term weighing 3300 g. He was breast fed for only two weeks. The father, who also has diabetes insipidus, is otherwise healthy and of normal intelligence, judging from his occupation and our correspondence and telephone conversations with him. The mother suffered from pulmonary tuberculosis at the time the boy was born and when he was 7 weeks old she was sent to a hospital and the boy placed in a pediatric hospital. The mother died shortly afterward and the boy has spent the rest of his life in hospitals and other institutions.

We studied all the records made during his stays in pediatric wards, which were from Aug. 31 to Oct. 6, 1942, from Feb. 25, 1943 to Feb. 8, 1944, from Aug. 17 to Dec. 8, 1944 and from Oct. 30 to Dec. 8, 1945.

Since Aug. 22, 1951, he has been kept in a boarding school for backward children, and we have also had access to the records there. In June 1956, he was admitted to a department of internal medicine for two days to find out his reaction to pitressin.

In our opinion, it is better to describe this case symptom by symptom rather than purely chronologically.

Polydipsia and polyuria.—The patient's abnormal thirst was mentioned for the first time in November of 1943 when it was said to be growing worse and worse. He

cried for water continually, and wet his bed all the time. From then on his large consumption of water was noted again and again. When he was 18 months old and weighed 8900 g, the amount of fluid he consumed daily was measured for a week and found to vary between 1850 and 1050 g. The figures probably represent the fluid he took between meals, but the records are not clear on this point. In December 1944, it was noted that he drank greedily anything drinkable, the contents of the wash basin or whatever else he could get at. The physician in charge of him at a children's home from the age of 5 to 9 years wrote: "He always drank by the liter and got up several times during the night to drink. If no clean water was on hand, he would drink the water out of vases and the urine from chamber pots."

Fever.—It was because his temperature rose so often for such long periods and for no apparent reason that the boy was admitted to the hospital on all except the first occasion. The attacks of fever began when he was 6 months old. From February of 1943 on and throughout the following year his temperature would stay at 38°C or higher for weeks at a time, and only for a few days or so was he ever quite free of fever. Peaks of 39.5°C occurred on several occasions. The next year the attacks grew more sporadic.

The tuberculin reaction was negative in test after test. In 1943 the lumbar fluid was examined and found normal. Pulmonary roentgenograms were normal. The Widal and Bang reactions were negative. He had occasional colds but on admission in 1943 after he had been feverish for four weeks he was free from catarrhal signs and symptoms. He continued to suffer from fever for which no infectious origin could be found, and "fever of unknown cause" was recorded in 1943 and 1944.

Vomiting and constipation.—From August 1943 to October 1945 the patient suffered from vomiting and poor appetite, especially for solid food. For weeks at a time he would have several severe attacks of vomiting per day and his general condition deteriorated and his weight decreased. Between these weeks he had periods when he did not vomit at all. During 1944 and 1945 he had attacks of constipation, though of mild degree.

Reaction to pitressin.—In August 1944, i.e., when the patient was a little more than 2 years old, he was given large doses of pitressin for ten days. During these ten days his temperature never rose above 37.5°C, and he seemed to be less thirsty. However, the treatment was not continued.

In June 1956, on our initiative, the boy was admitted to a department of internal medicine for two days' observation.[1] As concentration tests and others were made during these two days it was impossible to get any figures for the urinary output per day. The effect of pitressin was tested by the method described in 1945 by one of us (H. F.), i.e., the specific gravity and sodium chloride concentration were determined in half-hourly fractions of urine. It was then seen that the patient was clearly susceptible to the drug and it was also noted that he was less subjectively troubled by thirst when the pitressin was given.

Restriction of fluid.—In order to be able to understand this case properly, it is necessary, in our opinion, to realize the attitude that was taken to the boy's condition and how this affected the way he was treated. The condition was long diagnosed as "polydipsia" and not until 1945 was the diagnosis of diabetes insipidus made. Still at the end of 1944 it was noted that "the polydipsia seems to be mainly of mental origin". It was also noted that "he was not given any more fluid than normal children".

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[1] Courtesy of Dr. Allan Björkman, Upplands Väsby.

In October 1945: "Fluid was limited to a liter a day." In December 1945: "The uncontrollable thirst comes on as soon as the patient sees water."

Once during 1944 when the patient was treated with sulfathiazole, his weight rose from 8090 to 8870 g in 12 days. It may be assumed that during this period he got the greater quantities of fluid prescribed for patients receiving this drug.

Physical development.—The boy weighed 3300 g at birth. When he was 7 ½ months old he weighed 7000 g and when he was 1 year old 9700 g. After this, however, his weight stood still and then began to drop. When he was 18 months old he weighed 8800 g and at 2 years of age 8000 g. When he was 3 years and 3 months old he weighed 11.7 kg. When he was 8 ½ years old he was 121 cm tall and weighed 24.6 kg In June of 1956 when he was 14 he was 159 cm tall and weighed 40.5 kg.

When he was 7 months old he was described as small and thin but alert-looking. In the autumn of 1944 when he was a little more than 2 years old and admitted for the third time to the children's hospital, he was described as poorly and greatly atrophic, and the skin on his arms and legs could be lifted up in large folds. He was extremely pale and his appearance was dominated by his large head and large sunken eyes. He lay like a frog with his hips rotated outward. He was extremely small for his age.

Mental development.—When he was 1 year old he could not sit himself up or stand and was assumed to be retarded in development. When he was 1 ½ years old he could sit up but not stand up, and did not talk at all. In December 1944 when he was 2 years and 5 months old, he could only walk when he was supported and could only say a few words. He was lively but distinctly retarded.

When at the age of 7 he was to begin school, his Terman-Merrill I.Q. was found to be 52 and three years later he was admitted to a boarding school for backward children, where he still is. In 1951 his Terman-Merrill I.Q. was 62 and in 1953 it was 58. In 1954 his I.Q. with the Arthur Performance test was 68.

Other afflicted members in the family

Woman number 4 in generation II was admitted to a school for mentally deficient in 1922, i.e., when she was 10 years old. After six months there it was concluded that she could not be taught anything and she was sent home. It may be assumed that her I.Q. is below 50, probably below 40. Her relatives report that she drinks an extraordinary amount of water but she has never been examined at a hospital. Her mother says that she has to drink at least every three hours day and night. She gave the impression of being extremely feebleminded to the one of us who met her. The mother cannot remember now whether this daughter had long periods of fever, a particular tendency to vomiting or constipation as a small girl. She is not particularly small.

All the other afflicted members have been seen by one of us, except the boy's father, number 5 in generation II, with whom we have only had contact through letters and telephone. None of them are distinctly mentally deficient, but number 3 in generation I is 84 and suffers from severe senile dementia. The family did not want to undergo testing with a posterior pituitary preparation.

Discussion

The condition of the described child coincides in every respect with the one observed by several authors in small children suffering from nephrogenic diabetes insipidus. In our case, however, the patient suffered from the

pituitary form of the disease, susceptible to ADH. It is not clear why a syndrome characteristic of nephrogenic diabetes insipidus developed in this case. The question is, however, whether it might not have been due to the child having passed its life in various institutions. The routine is seldom so rigid in a home as it is in institutions; moreover we know that the water intake of this boy was deliberately rationed for several years.

The reason why this picture so seldom develops in the pituitary form of the disease, is still obscure. The four siblings in generation II who had diabetes insipidus may be assumed to have been brought up much the same. Only one of them is mentally deficient, and if this was because of the diabetes, the outcome has been very different for the different siblings. Perhaps it is partly because the disease varies in intensity that only a few of the afflicted persons are severely affected in infancy.

The case described herein may help to explain why the persons with nephrogenic diabetes insipidus become mentally retarded. It was suggested by one of us (H. F.) in 1955 that the backwardness may be the direct result of the gene on the cerebrum, in other words that it is a question of a pleiotropic gene. Now that feeblemindedness has also been observed in two cases of pituitary diabetes insipidus, inherited through an autosomal gene, this hypothesis is no longer plausible. Common to the two forms of the disease is the dehydration in infancy. It is probably the dehydration, therefore, that causes the mental deficiency in both instances.

This observation confirms once more how important it is to give all the children who have or might have diabetes insipidus copious amounts of water during their first few years. It seems to be particularly important to see that children who live in institutions get all the fluid they need.

Summary

The report concerns a family with autosomally inherited diabetes insipidus of the pituitary form. A detailed description is given of a boy who was hospitalized for long periods during his first three years and then showed the dehydration, fever, vomiting, constipation and retarded development hitherto only observed in the nephrogenic form of diabetes insipidus. The child, who is now 14 years old, has an I.Q. of 58 according to Terman-Merrill. One of his father's sisters, who also has diabetes insipidus, is severely mentally retarded.

In view of the fact that mental retardation has now been observed in two genetically different forms of diabetes insipidus, the authors reject the hypothesis of it being the effect of a pleiotropic gene.

The authors stress how important it is to include a copious amount of fluid in the diet of children who have or might have diabetes insipidus of any form.

Description d'un cas de diabète insipide génétique du type hypophysaire présentant l'aspect d'un diabète insipide du type rénal.

Cet article concerne une famille où l'on rencontre des cas de diabète insipide héréditaire du type hypophysaire chez des membres des deux sexes. Les auteurs décrivent en détail le cas d'un garçon qui avait été hospitalisé durant de longues périodes au cours des trois premières années de son existence et se mit alors à présenter les phénomènes de déshydratation, fièvre, vomissements, constipation et arriération que l'on n'avait jusqu'alors observés que dans la forme rénale du diabète insipide. Cet enfant, qui est maintenant âgé de 14 ans, présente un quotient intellectuel de 58 selon la table de Terman-Merrill. Une des soeurs de son père, qui est également atteinte de diabète insipide, souffre d'arriération mentale sévère. Puisque l'arriération mentale a désormais été observée dans deux formes génétiquement différentes du diabète insipide, les auteurs rejettent l'hypothèse d'après laquelle cette maladie serait due à l'intervention d'un gène pléiotrope. Les auteurs attirent l'attention sur l'importance de l'abondance des liquides dans le régime des enfants atteints ou susceptibles d'être atteints d'une forme quelconque du diabète insipide.

Ein Fall von genetischem Diabetes insipidus von hypophysärem Typus mit scheinbar nephrogenen Symptomen.

Der Bericht betrifft eine Familie mit autosomatisch vererbtem Diabetes insipidus von hypophysärem Typus. Eine eingehende Beschreibung eines Jungen wird dargeboten, welcher während der ersten drei Lebensjahre im Hospital behandelt wurde und die Symptome von Wasserverlust, Fieber, Erbrechen, Verstopfung und Entwicklungshemmung aufwies, wie sie bisher nur in der nephrogenen Form des Diabetes insipidus beobachtet worden waren. Bei dem gegenwärtig 14 Jahre alten Kinde beträgt der Intelligenzquotient nach Terman-Merrill 58. Eine Schwester seines Vaters, auch mit Diabetes insipidus behaftet, ist geistig sehr stark zurückgeblieben. Im Hinblick auf die Tatsache, dass geistige Hemmung in zwei genetisch verschiedenartigen Formen des Diabetes insipidus beobachtet worden ist, lehnen die Verfasser die Hypothese, dass er von einem pleiotropischen Gen bewirkt werde, ab. Die Verfasser betonen mit Nachdruck, wie wichtig es sei, reichliche Flüssigkeitsmengen in der Diät von Kindern mit ausgesprochenem oder vermutetem Diabetes insipidus, einzuschliessen.

Un caso de diabetes insípida genética del tipo pituitario simulando tipo nefrógeno.

En esta relación se expone el caso de una familia presentando diabetes insípida autosoma hereditaria en forma pituitaria. Se describe detalladamente el caso de un niño hospitalizado por largos espacios de tiempo durante sus tres primeros años de edad y que luego manifestó la deshidratación, fiebre, los vómitos, estreñimiento y desarrollo atrasado, observados hasta entonces en la forma nefrógena de la diabetes insípida. El niño, que cumple en la actualidad 14 años de edad, tiene un I.Q. de 58, de acuerdo con Terman-Merrill. Una de las hermanas de su padre, que también padece diabetes insípida, presenta un severo atraso mental. En vista del hecho de que ahora el atraso mental ha sido observado en dos formas genéticas distintas de diabetes insípida, los autores refutan la hipótesis de que pudiera tratarse de los efectos de un gen pleotrópico. Los autores subrayan insistentemente la importancia de incluir una cantidad copiosa de líquido en la dieta de los niños que manifiesten, o puedan manifestar, cualquier forma de diabetes insípida.

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Received December 21, 1956

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Acta Pædiatrica **46**: 301—302. May 1957

From the University Clinic of Pediatrics, Rigshospitalet, Copenhagen
(Chief: Prof. P. Plum, M.D.)

Collection of Urine in Infancy by Means of Plastic Colostomy Bandage

by JØRGEN VESTERDAL

Collection of urine from infants, particularly girls, frequently causes trouble. If the urine has to be collected for 24-hour periods this may be really difficult.

In the University Clinic of Pediatrics, Rigshospitalet, Copenhagen, the following device, suggested by Miss Edith Qvist, R.N., has been used in recent months:

A plastic colostomy bandage[1] with an adhesive surface (Fig. 1) is used.

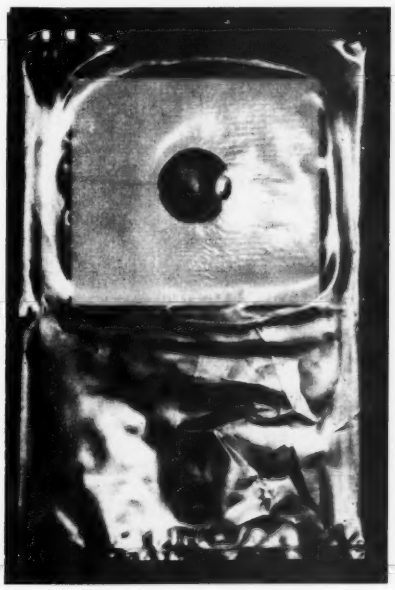

Fig. 1. Plastic colostomy bag.

[1] "Coloplast", to be obtained from *Dansk Plastic Emballage*, Gladsaxevej 311A, Søborg, Denmark.

Fig. 2. The adhesive surface is glued to the skin round the genitals.

Fig. 3. The anus is kept free.

The adhesive surface is placed round the genitals and glued to the skin (Fig. 2) while the anus is kept free (Fig. 3).

This procedure may be used for both sexes and permits collection of urine for 24 hours without admixture of feces. If the urine has to be collected for more than one day, it is not necessary to remove the plastic bag: the emptying may be carried out through a small puncture done with a needle; afterwards the puncture is closed with adhesive tape.

Summary

A simple method is described for collection of urine from infants of both sexes by means of a plastic colostomy bag.

Accepted January 24, 1957

Pediatric Clinic
Rigshospitalet
Copenhagen, Denmark

Acta Pædiatric 46: 303–314. May 1957

The Norwegian Pediatric Society

Meeting in Bergen, May 11 and 12, 1956

Frithjof Wigers: **Bergen one hundred years ago. A social-clinical survey.**

With the aid of a few figures and quotations the author has endeavoured to give a picture of the city of Bergen one hundred years ago, with special reference to social and social paediatric conditions, At that time Bergen had 26,000 inhabitants, with 22 per cent in the age group below 10 years, while at present it has 112,000 inhabitants, with only 15 per cent in this age group. At that time there was a marked distinction between the lower and upper social classes, a distinction which also extended to the Church, where the children of the common man were baptized in a brass basin, while a silver one had to be paid for. The alcohol consumption then was more than double that of today. The birth rate was about 30 per mill, and all children were born in their homes. Today the birth rate is 15 per mill, and birth at home is an exception only. The first day-nursery was founded in 1840. The schools were over-crowded, and religious instruction played an important role. It was given in a manner too difficult for children to grasp properly.Wet nurses from the surrounding districts were much used by the upper classes. The poor milk hygiene partly explains the high rate of infant mortality, viz. 150–170 per mill, and a remarkably high number of these were reported to have died from "convulsions". For the age group 1–10 years, and with the same rate of mortality, we should today expect 500 deaths annually. In reality we have a dozen. No rule without exception, however: Gerhard Armauer Hansen, who discovered the lepra bacillus, was one of fifteen siblings, all of whom reached mature age. Finally, the author stressed the importance of judging each period against the background of its own total cultural pattern.

K. H. Torp: **Giant haemangioma and thrombocytopenia.**

A few cases of this syndrome in infants have been published in the course of recent years. This combination was demonstrated in a 10-month-old female infant, who was observed in the Paediatric Department, University of Oslo. The hæmangioma had been first noticed when the infant was two months old. It had since been increasing steadily. On admission the hæmangioma involved the entire occipital region and the vertical region almost to the coronal suture. The extent was estimated at $18 \times 16 \times 1\frac{1}{2}$ cm. It was partly cavernous, partly capillary. The parents had noticed that in a total of four brief period of 2–5 days during the past four months, the hæmangioma had a swollen and firm appearance, and the adjoining temporal regions, forwards to the forehead, were very oedematous, and showed localized purpura. On admission the blood count showed normal findings, apart from the thrombocyte figure, which was 23,900, and the bleeding time which was prolonged, 20 minutes. Residual haemor-

rhages were present in the skin, in the forehead and in the temple. Analyses of bone marrow showed normal megakariocytes, and no antibodies to thrombocytes were demonstrated in the serum of the patient. During the two months hospitalization the thrombocyte figure was counted daily, and for long periods was found to lie between 10,000 and 20,000. Some days, however, apparently spontaneous increases were recorded of the thrombocyte figure, up to 70,000 and one one occasion up to 200,000. In an attempt at elucidating the pathogenesis of the thrombocytopenia the following experiments were performed:

1. During periods when the thrombocyte figure was steadily below 20,000, an elastic bandage was wound tightly round the head and back of the neck, in order to occlude, or at any rate to change the blood stream through the hæmangioma. At the first attempt the thrombocyte figure increased from 9000 before compression to 129,000 after compression for three days. At the second attempt the thrombocyte figure increased from 12,000 before compression to approximately 100,000 after compression for six days. This latter compression was so powerful that a couple of necroses appeared in the skin of the forehead. Due to the demonstrated tendency to spontaneous variation in the thrombocyte figure, it is not convincing that the compression of the hæmangioma should be the cause of the improvement in the thrombocyte figure—which was demonstrated at both attempts.

2. No doubt the infant had pathologically enlarged veins in the temples, particularly in the right temple. These were supposed to be probable drainage veins for the hæmangioma, at any rate from the anterior part of the hæmangioma on each side. Simultaneous thrombocyte counts were performed in venous blood in the general circulation, as also in blood from these hypothetical drainage veins. Furthermore, blood was occasionally taken directly from the hæmangioma for such comparative analyses.

All examinations—with one exception—showed the same number of thrombocytes in the drainage veins and in the general circulation. One single examination, however, showed that the platelet figure in the adjoining drainage vein on the right side, was significantly lower than in venous blood on the back of the hand. This may be interpreted to mean that thrombocytes in period are "caught" in the hæmangioma, and in these periods are found, therefore, in reduced number in the drainage veins. This concept is supported by the fact that this definite difference was demonstrated at a time when the thrombocytes of the infant generally showed a falling tendency. All thrombocyte counts during these special experiments were made in double specimens, by direct counts. The infant was given X-ray irradiation to the hæmangioma with dosage 500 r, and when she was 17 months of age the hæmangioma had shown marked regression, and the platelet count was normal. There had been no purpura in the course of the past six months.

Roald Rinvik: **Idiopathic hypercalcaemia.**

Two types of idiopathic hypercalcaemia have been recognized. One mild and benign form is self-limiting and has a good prognosis after a brief course. This form shows no congenital malformations, which however seem to be associated with the second type, which also has a long and severe course. In this type physical and mental retardation is frequently found, as also other abnormalities. The severe type was first described by Fanconi and Butler, the benign type by Lightwood, both types in 1952, the latter entitled "Hypercalcaemia with failure to thrive".

In both forms anorexia, feeding difficulties vomiting and constipation seem to be the main symptoms, and ordinarily the disease commences at the age of 6–12 months. In both types we find increased serum calcium. Sometimes there is an increased amount of blood cholesterol even in the benign forms. Hypercholesterolaemia, however, is always present in the malignant type, and azotaemia is also found constantly. These patients further develop a typical appearance with small skull, low nosebridge, ears placed lower than usual, and protruding maxillae. Hypertension and a systolic murmur on heart auscultation are common findings. X-ray examinations show osteosclerosis in many of the bones. The conditions seems to be fatal, and severe renal changes are revealed at autopsy. This disease is observed practically solely in Great Britain.

In the differential diagnosis we have to consider hyperparathyreoidism and vitamin D intoxication, which have been discussed as an important etiological factor in the disease. Bonham Carter gave calciferol 10,000 units daily for ten days, and his conclusion was that there was an abnormal sensitivity to vitamin D based upon a coincident clinical deterioration in one of his patients.

A 15-month-old boy with idiopathic hypercalcaemia was demonstrated. He was operated on at the age of 4 months for a bleeding Meckel's diverticulum, and his hypercalcaemia symptoms seem to have commenced at the age of 6–7 months. He presents the typical appearance, and besides hypercalcaemia there is hypercholesterolaemia and constant azotaemia. At the first examination the only objective symptom demonstrated was marked general hyperreflexia. He had a systolic murmur, and X-ray examination disclosed extensive calcifications in the skeleton, but no renal calcifications.

He was treated with cortisone with excellent effect. Subsequently a calcium-free or calcium-low diet was given, apparently with equally good results. During this period he was also given cod liver oil for several weeks, 10–20 g daily (some 1500 units), and showed steady clinical improvement despite persistently high serum calcium level. The blood findings are practically unchanged, the effect of the treatment seems to have been mainly clinical. The patient is still under observation.

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Johan Olsen: **Hypophosphatasia.**

Recently a new disease has been recognized, which is related to diminished activity of alkaline phosphatase. Alkaline phosphatase activity is normally found in practically every tissue, but especially in calcifying bone, intestinal mucosa, renal cortex and lactating breast tissue. The disease was first described by Rathbun in 1948; a 3-week-old boy had already developed rachitic bone lesions; diminished alkaline phosphatase activity was demonstrated in serum and in different tissues. Sobel *et al.* in 1953 described a 19-month-old girl with rachitic bone lessions, genu valgum, premature loss of deciduous teeth, and low activity of alkaline phosphatase. Additional cases have been reported.

From the Paediatric Department, University of Bergen, one case is described: A girl, 11 months old, commenced shedding her teeth, and when 4 years old had only the molars left. The patient was mentally retarded. The "Anlage" for the permanent teeth was present. The alkaline phosphatase activity in serum was constantly low, 1.7–1.8 Bessey–Lowry units. The serum calcium and phosphorus were within normal limits.

No bone lesions were demonstrated. Her 8-year-old brother also had low alkaline phosphatase activity in serum, 2.3 Bessey–Lowry units. In hypophosphatasia different kinds of therapy have been tried without success.

Kr. Harnæs: **Some remarks on the treatment of bacterial allergy.**

Bacterial allergy plays an important part as the causal relation of bronchial asthma in children, particularly in early infancy. The history with attacks of asthma associated with infection of the upper respiratory tract, together with negative result of cutaneous tests, are the main data on which to base the diagnosis. A distinct general reaction on small doses of anticatarrhal vaccine also speak strongly in favour of bacterial allergy. In more severe cases of bronchial asthma on bacterial basis desensitization with anticatarrhal vaccine is recommended. A scheme describing the procedure followed at the Paediatric Department, University of Oslo, was shown.

R. Amlie: **Vitamin B_{12} as an appetite-stimulating factor.**

In a selected group of patients from a health station, consisting of under-nourished children, vitamin B_{12}—given as a cherry-flavoured syrup—was found to increase the appetite and produce a rise in height and weight. Conditions in which response was good, was when the child had a very poor appetite in convalescence after rhinopharyngeal or gastrointestinal infections of long duration, or had resisted feeding for some time. The effect of the medication could be explained as a treatment of a hypovitaminosis due to poor consumption of animal protein. The syrup contained 30 μg vitamin B_{12} per teaspoonful, and was given twice daily. Good response was obtained in 8 cases, in some of which the effect was extremely rapid. Infants in the first year of life showed no response. It was supposed that the medication might be valuable in cases of poor appetite, because the hypovitaminosis in itself would reduce the appetite, so that in that way a vicious circle could be broken.

A. Drablös: **Oligophrenia phenylpyruvica (Fölling): Treatment by diet.**

In Fölling's disease the phenylalanine concentration of the plasma is increased to about 10–20 times the normal value. Results show that food containing little phenylalanine will bring the plasma level down to normal values. As source of protein during this diet, a casein hydrolysate free from phenylalanine can be used. The amino acids tyrosine and tryptophan have to be added because these are lost during the preparation of the hydrolysate. The small amounts of phenylalanine which are necessary for the synthetizing of the proteins, can be given as milk (about 150 ml daily).

At the Paediatric Department, University of Bergen, two cases have been treated with food containing little phenylalanine.

The first case which was highly oligophrenic, was a boy 2 years old when the treatment started. He was on this diet for 10½ months, and a fairly good normalizing of the phenylalanine values in serum and urine was obtained (analyzed microbiologically and by paper chromatography). The increase in weight was normal, and no certain symptoms of nutritional deficiency were observed. His mental condition was easier and more quiet for a couple of months, and his interest in his surroundings increased greatly. After some time, however, there was no further progress, and the progress achieved was considered to be too small to be of any practical importance. After the diet had been stopped, the patient again grew more debile, and his previous frequent crying recurred.

The second case, also a boy, was only 8½ months when treatment began. He seemed slightly psychically affected. He was given the diet for three months, and during this time no mental change of any kind was observed. His condition was complicated by a hip joint luxation, which was treated with a plaster cast. Rhonchi were heard constantly at the base of both lungs, with periodical rise in temperature. One morning the patient was found dead in bed. Death had been caused by aspiration of vomited stomach content. Autopsy showed otherwise a strongly marked fatty liver.

Based on cases published and on his own experience, the author has drawn the following conclusion concerning diet treatment of Fölling's disease: The diet is as yet too expensive for regular use. The casein-hydrolysate has a very astringent, unpleasant taste, which makes the treatment very hard to complete. The diet which is very rigorous, demands constant supervising of the patient, and yet can hardly be claimed to be harmless. It is very doubtful whether this diet offers good enough result in infants and older children to be of any practical value. As far as infants are concerned, however, no complete experiment has been reported as yet, and there should be a chance of better results, therefore, when the treatment is instituted at a very early stage of the disease.

H. Moestue: **Electrolyte determination in sweat as diagnostic test in cases of fibrocystic disease of the pancreas.**

In collaboration with the Biochemical Laboratory of the University Hospital, Bergen, determinations have been carried out of sweat electrolytes in 22 children in the Paediatric Department, University of Bergen, since the autumn of 1955. A slightly modified technique, the method of Schwachmann, has been used. According to Schwachmann sodium values higher than 80 mequ/l are strongly in favour of the diagnosis of fibrocystic disease of pancreas (*Paediatrics*, 1955). Eleven of the 22 cases analyzed were patients with no organic disease, aged between 4 months and 10 years. They showed normally low values. Two patients with coeliac disease also showed normal values. The investigation also comprised one case of proved fibrocystic disease, his mother, one sister and two brothers of the patient being also examined. The father and one healthy sister had not been examined. The mother, who had been pregnant fourteen times, and had given birth to 11 children, had normal sodium and chloride values in sweat. The patient with fibrocystic disease of pancreas showed sodium and chloride values of 119 and 122.6 mequ/l respectively. His two brothers had highly abnormal sodium values, viz. 184 and 185 mequ/l, while the sister had normal values. Six of the 11 children died, one daughter when 6 weeks old, in convulsions.

The following retrospective diagnoses seem justified with regard to the other 5 children who died: Meconium ileus, 1 case; transitory meconium ileus and fibrocystic disease of pancreas with subsequent pulmonary disease, and death at the age of three months, 1 case; fibrocystic disease of pancreas with pulmonary complications, 3 cases. These children all died from pulmonary disease ("penumonia") when about three months old.

Arne Kåss and K. Fr. Støa: **Quantitative determination of fatty stools in children.**

The method of van der Kamer and co-workers for quantitative determination of fatty stools was used for analysis of 109 faeces samples from 75 patients: 44 of whom were children of various ages, without intestinal complaints, on ordinary diet according to age, 11 patients with dyspepsia without fatty diarrhoea, and 18 patients with stea-

torrhoea. Even though the material is relatively modest, it seems to demonstrate distinctly that the values usually regarded as normal limit of excretion of fat in the stools of children (2 g per twenty-four hours), are too low. Unexpectedly great variations in excretion of total fat were found in the "normal" material; average excretion was found to be 4.8 g per 24 hours, and 80 per cent of the "normal" children excreted more than 2 g of fat each twenty-four hours. The total excretion of fat was found to be on an average considerably higher in steatorrhoea patients, particularly the untreated ones. In these, however, as well as in patients under treatment, there was so great variability in the values that this circumstance, also considered in correlation with the great "normal" variation reduces the usefulness of quantitative determination of fatty stools in steatorrhoea patients, in diagnostic respect as well as for the evaluation of therapeutical effect. The amount of split fat varied somwehat in the different groups of patients, though the difference was of no statistical significance. The percentage of fat in dried faeces was also found to be far higher than the 10–20 per cent usually recorded as normal values. In infants up to one year of age an average of 50 per cent of fat was found in dry material. With increasing age a falling percentage of fat was found. Only in patients over the age of 5 years was the predominating number of samples in the test material found to contain below 20 per cent of fat. In the 34 samples from the normal material of children below 5 years of age, the age group in which we are particularly interested to carry out quantitative determination of fat in stools, 32 samples (94 per cent) had more than 20 per cent of fat in dried material. It seems as if our concept of fat excretion in children on usual standard diet, will have to be revised, and that only fatty balance test will be of real value. Routine observation of fat excretion in the stools of steatorrhoea patients must also be regarded as having very limited value.

H. Hagelsteen and S. Eek: **Twisting of the stomach as cause of vomitings in infancy**

Improved technique of X-ray examination of the stomach in infants has shown that vomiting, which previously has been registered as neuropathic or habitual, is due largely to anatomical changes or disturbances of the vegetative nervous system. Several typical entities of disease have been separated from the group of habitual vomitings. Most familiar are the different forms of duodenal stenosis, and various anatomical and physiological abnormalities of the oesophagus and the cardiac region, such as oesophageal achalasia and chalasia, oesophageal hernia, short oesophagus, and so forth. A cause to which less attention has been given, is change in position of the stomach, observed in association with a distended, gas-filled and interposed transverse colon. The history of disease is always typical with vomiting, generally projectile vomitings, with onset just after birth, most frequently during the first days of life. X-ray examination shows that the stomach has pathological shape and position. The fundus and the pyloric part lie in their normal position, while the corpus part is elevated by the gastrocolic ligament of the gas-filled and distended transverse colon, which is interposed between the anterior abdominal wall and the liver. Thus, the greater curvature of the corpus becomes the highest part of the stomach, and with the patient in supine or erect position the content of the fundus first has to pass "uphill" in order to reach the pylorus, which points almost straight distally, or distally and slightly to the right. It is also supposed that the gastric peristalsis is disturbed, and is thereby conducive to the occurrence of vomiting. If this concept of the etiology is correct, the stomach should slip back to its normal position, and the emptying conditions become

normal, when the patient is placed with the upper part of the body lowered, so that the gas-filled colon slips caudally. X-ray films of one of our patients show very clearly that this takes place. Roviralta in 1949 emphasized that prone position with the upper part of the body lowered, was the only treatment required. He has described the condition and used the designation "la plicature de la grande courbure de l'éstomac" —a designation which is purely descriptive, making no mention of the cause. We have preferred, therefore, to call the condition twisting of the stomach. No doubt it is not a rare condition. History of disease and X-ray findings are typical, and the therapy is effective.

(Five cases are recorded, with demonstration of X-ray films.)

R. Savosnick: **Recurrent parotitis.**

The first attack of mumps is considered to give lasting immunity, and the possibility of a second infection with parotitis virus is improbable. It happens nevertheless that a child with swelling of the parotid gland is diagnosed as having epidemic parotitis in spite of the fact that the child has had mumps previously. In such cases other causes should be looked for. A lesion which clinically shows complete resemblance to epidemic parotitis, is recurrent bacterial parotitis. This is not a rare lesion, but it is evidently little known. The diagnosis is easily established, if the lesion is known. The main criteria to show that it is bacterial and not virus parotitis, are the following: inspection of Stensen's duct discloses rubor and oedema, and pressure and massage on the swollen parotid gland produce mucopurulent, "snow flocculated" saliva, microscopy of which reveals leucocytes and bacteria. Further, a sialogram will demonstrate dilated glandular ducts and ectasis in the peripheral parts of the gland (sialectasis). These dilated glandular ducts are regarded as an etiological factor. Congestion of secretion occurs, thereby increasing the possibility of ascending canalicular infection from the oral cavity. When first stagnation has occurred and sialectasis has developed, predisposing factors are bacterial foci such as carious teeth, infected tonsils, or pathogenic microbes in the oral cavity. Some authors have claimed that in addition to bacterial etiology an allergic factor must also play a part, and that some cases of recurrent parotitis are due to obstruction of the ducts due to spasm and oedema.

One case is recorded, a 5-year-old boy, with recurrent parotitis associated with recurrent thrombopenic purpura. In this case the possibility of both bacterial and allergic etiology has been considered.

As the infection is ductogenuos, the most effective treatment is to inject antibiotics straight into Stensen's duct. Stagnation of saliva may be prevented by massage of the parotid gland, and by a diet demanding vigorous chewing. Infection foci in the oral cavity must be treated.

Roald Rinvik: **Some reflections on acute nephritis.**

An account has been given of the material of the past five years from the Children's Department at Ullevål Hospital, Oslo. The total number of patients is 132, 58 girls and 74 boys. The majority of cases is in the age group 3–7 years, which covers more than two-thirds of the total number. Only one patient was under two years old. In the majority of the patients the disease has its onset in the winter season: 63 cases in the fourth quarter and 33 cases in the first quarter of the year. With regard to the symptoms 60 of 132 patients showed on admission a urea level in blood of more than

40 mg %, 39 of whom more than 50 mg %. Forty-five patients showed systolic blood pressure of more than 130 mm on admission. None of the patients had convulsions, and light uraemia symptoms were noted only in connection with the azotaemia. Too much attention should probably not be paid to the hypertension, as practically all of these patients showed normal figures after some days, and only in three did the hypertension, which was moderate, persist for some weeks. Practically all the children showed increased sedimentation rate, only 9 below 15 mm, 63 more than 50 mm. Antistreptolysin titers of more than 250 were registered in 97 of 132 patients, the highest figure being 4000.

A follow-up examination was carried out in 94 patients, at least 6 months after discharge. Eighty of them showed normal Addis count on discharge or later, and ten patients showed normalized findings during the first month after discharge. Two patients had a relapse, but were subsequently cured, while 2 of 94 patients—a little over 2 per cent—turned into a chronic phase.

It was also discussed why the incidence of nephritis had increased so remarkably during recent years. Further subjects of discussion were: principles of treatment, bed rest of long duration, or not, questions of prophylaxis, and so forth.

Bjarne Smeby: **Purpura allergica: Survey of a series.**

During the period autumn 1950 to spring 1956 a total of 25 children suffering from purpura allergica (15 boys and 10 girls) were admitted to the Paediatric Department, University of Bergen. Ten children were aged from 2–4 years, 13 children had not yet reached the age of 4 years. The children were admitted the hospital on an average 8 days after the first symptoms of purpura had occurred, and they stayed in the hospital for 28 days averagely. Twelve patients had a family history of allergy, 6 patients had a history of previous allergic diseases. Five families gave a history of rheumatic lesions, and their children had affections of one or more joints during the disease. All children below the age of 4 years had infection of the upper respiratory tract prior to, or concurrent with, the purpura allergica. Infection was found in 22 of 25 patients. In 10 patients gastrointestinal symptoms were the first manifestations of purpura allergica. Another 7 patients had skin haemorrhages, 7 had swelling of joints, and one patient had oedema. Two boys were operated on under the diagnosis of acute abdomen, but intestinal haemorrhage only was demonstrated. Thirteen children had normal urine, 12 children had symptoms of renal affection. The urinary abnormalities were generally found on about the thirteenth day. Four children developed acute nephritis, one of them died of anuria on the thirty-seventh day after the onset of the disease. Twenty patients had exacerbations, consisting of fresh skin bleedings, abdominal pain, joint affections, and/or renal abnormalities. In 21 of 25 patients complete follow-up examinations were carried out.

Follow-up examinations were performed in 4 patients about three months after they had left the hospital and in the other 17 children on an average 2½ years after their discharge from the hospital. One patient was found to have chronic nephritis, another patient arterial hypertension. Morning urine of 21 patients was examined for proteinuria, and in 18 of these also the day's urine. Pathologic urine was demonstrated only in the patient with chronic nephritis. This would seem to indicate that the incidence of orthostatic proteinuria is not higher in these patients than in others. Four patients of the control series had fresh skin bleedings, one of which reported that he had skin bleedings once monthly for about four years.

Alfred Sundal: **Acrodermatitis enteropathica (Danbolt-Closs) and Diodoquin treatment.**

Acrodermatitis enteropathica was described as a clinical entity by Danbolt and Closs in 1942. Previously the disease had been designated: atypical bullous epidermolysis, generalized moniliasis, or acrodermatitis continua Hallopeau. The disease is often familial. It commences most frequently at the age of 1 month to 18 months, generally when the child is weaned and is given addition to the mother's milk. In the pronounced cases skin affection occurs with vesicobullous groups in the skin, with predilection for the natural orifices of the body, and on fingers and toes. Loss of hair occurs (head, brows and lashes); usually there are also gastrointestinal symptoms with periods of diarrhoea and fatty stools. The general condition deteriorates, spirits are low, anorexia and photophobia occur. The skin lesion and the diarrhoea have a course with remissions and exacerbations. After Schlomovitz had suggested treatment with Diodoquin (dihydroxyquinolin), excellent results were obtained by this treatment. The author reports two siblings with acrodermatitis enteropathica, in whom various forms of treatment had failed, and where Diodoquin has cured all symptoms, without exacerbations during a nine-month period of observation. The study will be published in 1957 in *Annales Paediatricae Fenniae.*

Jogeir Hvidsten: **A follow-up study of enuresis patients.**

A follow-up study has been made of enuresis patients treated in the Paediatric Department, University of Bergen, in the period 1950 to 1953 incl. Patients with enuresis as well as encopresis have been excluded, as also patients with mental retardation as well as enuresis. Further patients have been excluded with whom the bed-wetting during their hospitalization has been of minor importance. The material consisted of a total of 94 patients, 56 boys and 38 girls. It has been possible to collect information from 82 of these patients. The follow-up study gave the following results: cured: 8.5 per cent, recurrence of wetting after a dry period: 28.7 per cent, and continous wetting after the stay in hospital in 50 per cent. A total of 35 per cent of the patients treated were below 7 years of age at the time of hospitalization. Environmental damage was pointed out in 32.9 per cent. The author supposes that hospitalization before the age of seven years, as well as the high incidence of environmental damage shown in these patients, have had an unfavourable influence on the results of treatment, (to be published later in detail in a Scandinavian medical journal).

Margrethe Wehn: **Pheochromocytoma in a six-year-old girl.**

After Labbé and coworkers in 1922 first described the clinical picture of pheochromocytoma, several hundreds of cases in adults have been recorded, while only 24 cases in children under 14 years of age have been published. The lesion is fatal in children, if left untreated. In recent years, however, we have been supplied with diagnostic and therapeutical resources, which improve the prognosis essentially.

Personal case.—In the course of two months a six-year-old girl developed a dramatic picture with periodical attacks of pain in the stomach, throat and back of neck, loss of weight, hyperhidrosis, constipation, polydipsia and paleness. After hospitalization her blood pressure became moderately increased. Convulsions of focal character occurred, giving suspicion of an intracranial expansive process. Palpation of the abdomen elicited attacks of pain, and the blood pressure rose to 210/180. Thereupon there was persistent, but variable hypertension. She was greatly exhausted, with constant attacks

of pain and marked peripheral vasomotor changes. The regitin test was positive. Electroencephalogram was strongly pathological with very irregular background activity, consisting of delta waves without focal character. Urinalysis showed very greatly elevated excretion of adrenalin. The patient was given premedication with regitin perorally for 120 hours, whereby the blood pressure was kept around 140/100. The condition improved considerably. A right-sided tumour was removed by surgery, and microscopy revealed the typical picture of a pheochromocytoma. During the operation and in the course of the following twenty-four hours she was given noradrenalin intravenously. The course was uneventful. Complete recovery.

Pediatric Society of South Sweden

Meeting, June 3, 1956

S. Widell: **Protein studies of the spinal fluid in abacterial meningoencephalitis.**

The amount of liquor protein and its composition has been examined in 40 healthy children of various age groups and in 52 cases of acute abacterial meningoencephalitis. The total protein content has been determined according to the method of Izikowitz: The composition of the protein has been examined by means of paperelectrophoresis according to Turba and Enenkel's method. In 23 normal cases aged over 1 year the liquor had a total protein content of 14–24 mg % (average 19 mg %). The variations were due principally to differences in the content of albumin: in liquor with low total protein content the electrophoresis showed a low albumin per cent, while the contrary was true in liquor with high content of total protein. Seventeen normal, fullterm infants below 1 year of age showed great variations of the protein content of the liquor, especially during the newborn period (45–120 mg %). After gradual decrease the amount of total protein did not attain the level of 1 year of age before 9 months. The electrophoresis showed during the newborn period high albumin content, often higher than in simultaneously examined serum, moderate increase of the gammaglobulin while the beta-globulins were decreased. The relatively high albumin level remained increased as long as the total protein content was increased, i.e. about 9 months. In the 52 cases of abacterial meningoencephalitis the content of the total protein at the first examination of the liquor varied roughly with the seriousness of the clinical symptoms. The pattern of the electrophoretic curve seemed, however, to be less dependent upon this factor than upon the time interval between the beginning of the symptoms and the lumbalpuncture. Cases that were punctured early showed relatively strong increase of the albumin content, during the first day of illness often surpassing the value in the simultaneously examined serum sample, while in the late punctured cases the increase of gammaglobulin was striking. In 27 cases which were re-examined after 2–3 weeks the total protein content had markedly diminished generally, however, without being totally normalized. The relative albumin content had decreased, sometimes to subnormal values while the gammaglobulin content had increased strongly (average about 50 per cent). The patients who had remaining subjective symptoms such as headache, fatigue, irritability etc. had also shown the most marked gammaglobulin-increase. In most cases the total protein content and the electrophoresis pattern had been normalized after 4–6 weeks but in some cases the gammaglobulin-increase had remained up to 4 months. All these patients had remaining clinical symptoms as mentioned above.

John Ingvar Ek: **Cerebral lesions in arthrogryposis.**

This condition has been considered as a peripheral disease and in the first hand has been treated as an exclusively orthopedic condition. Several speculations as to its pathogenesis have been published. One of the better known is Sheldon's concept as a muscular "Anlage-defect". Some authors have also considered the possibility of central nervous lesions, especially spinal lesions. Cases have been reported in which atrophy of the frontal horn cells in the medulla has been found at post-mortem examination. At the pediatric clinic of Lund 4 typical cases of arthrogryposis have been treated during the last 6 months. Two of these had evident signs of a gross organic cerebral illness and the other patients also probably had cerebral lesions. In the two first mentioned cases defects in the brain corresponding to those in porencephalia have been shown with encephalography. In the two other cases no such neurological findings had been made. These two patients had, however, intelligence defects of such severity that an organic cerebral lesion in all probability exists.

Meeting, November 18, 1956

Stephan Vendel and Ib Boesen: **Congenital heart defects in early childhood.**

At Queen Louise's Children's Hospital in Copenhagen during 1955–56 a total of 150 children under 2 years of age (27 were younger than 1 year) with congenital heart disease were examined. In addition to the general clinical examination, cardic catheterization and angiocardiography were carried out (the technique is described in *Brit. Heart J., 18:* 355, 1956). Among the 127 infants 41 (= 31 %) were found to be operable. Of these there were 17 with Fallot's tetrad, 3 with coarctation of the aorta, 4 with pulmonic stenosis, 9 with atrial septal defects with sinistrodextral shunt and 8 with persistent arterial duct. In addition there were 41 patients with ventricular septal defects with sinistrodextral shunt, of whom 38 had considerable pulmonic hypertension. Twelve of these patients underwent the pulmonary constriction operation proposed by Dammann and Müller (the preliminary results are published in *Bull. Soc. Internat. Chir.*, no. 5, 1956, and *Danish Med. Bull., 3:* 197, 1956).

It is concluded that with the combination of general clinical examination, cardiac catheterization and (preferably selective) angiocardiography great diagnostic certainty can be attained even in infants and that about one third of the examined infants have operable cardiac defects. This should also be expected from the author's earlier published autopsy studies of infants with congenital heart disease (*Acta paediat., 44:* 392, 1955).

Ulla Claesson: **Rubella and purpura.**

During a rubella epidemic in the city of Malmö with 1203 reported cases, complications with thrombocytopenic purpura occurred in 3 children. Thirteen such cases have previously been described in the literature. All 3 cases exhibited uniform symptoms and largely the same course as the cases earlier described. The disease appears on the third to eleventh day after rubella and is manifested by hemorrhages in the skin and mucous membranes of more or less alarming type. The initial thrombocyte value is usually low, *c.* 10,000–20,000. The course is as a rule mild, often with complete regression of the clinical symptoms within the first week without any special therapy. One death from a cerebral hemorrhage, however, is described. Blood transfusions should be

resorted to in the acute phase. No correlation has been found between the degree of severity of the primary disease and the extent of the hemorrhages. The thrombocytes were examined in 16 patients with uncomplicated rubella in the exanthematous stage and after 3 weeks. These cases showed on the average 40 % lower values in the first count. Thus in many cases of rubella the thrombocytes are affected; although only in a few to such a high degree that a manifest purpura occurs.

J.-C. Encrantz: **Toxic renal damage after Tridione medication.**

A 6-year-old girl, who had been treated for 9 months with 200 g Tridione for petit mal, developed albuminuria, which lasted for 19 days after the drug was discontinued. Electrophoretic examination of the serum revealed a nephrotic picture with reduction of the albumin to 1.4 % and of the total protein to 4.4 %. The serum-calcium was decreased to 7.6 mg %, the alkaline phosphatases were increased to 15 units (Bodansky) and the srum-phosphorus to 4.9 mg %. In a control examination 2½ weeks later these values had become almost normal. The patient did not have any noticeable edema, and the presence of a latent edemic condition could not be ascertained from the body weight determinations. According to Atchley the nephrotic syndrome is characterized by edema, albuminuria and reduced plasma albumin. Nine cases with certain or probable nephrotic symptoms after Tridione treatment have been found in the literature.

John Ingvar Ek: **A maternal factor in mongolism.**

Mothers of mongoloid children have been examined for objective indications of a disposition toward thyroid dysfunction. According to the author such symptoms are a pathologically palpable thyroid gland or an abnormal value of the protein-bound iodine in the serum (PBI). The cases investigated comprised 21 mothers of children who were born after January 1, 1951 and have been hospitalized in the Children's Clinic in Lund under the diagnosis of mongolism. The examination consisted of careful recording of anamnestic material, especially gynecologic data. With respect to the PBI the mothers were questioned as to eventual use of medicine or X-ray examination. The physical examination was generally limited to palpation of the thyroid gland and in certain cases measurement of the blood pressure and physical examination. In addition all observable clinical signs of hypo- or hyperthyroidism were recorded. The youngest of the mothers was 19 years at the birth of the mongoloid child, and the oldest was 47 years old. The average age at the actual parturition was 37.4 years. The period which elapsed between parturition and the time of the examination, which generally took place during September and October 1956, was on an average 2.4 years. Nine of the 21 mothers had struma. This was recorded for 4 patients in journals from other clinics. The PBI in 3 of the women was pathologically increased, i.e., above 8 γ %. The mean value for all the women was 7.1 γ %. This value differs significantly from the mean value of a group of normal individuals ($P < 0.001$). No case had a value of less than 5 γ %. The lower limit of the normal variation, corresponding to approximately 3 sigma, was 4 γ %. No certain clinical indications of hyperfunction could be demonstrated in those examined. The suspected cases, however, have not yet undergone a comprehensive examination regarding basal metabolism, cholesterol in the serum or isotope studies, etc. The frequency of abortion among the mothers was at least 20–25 %. Relatively often the mothers were primigravidae, especially those in the age group over 40 years, where no less than 4 of 9 had not earlier given birth to a child. One of the mothers had 2 children, both of whom were mongoloid.

Acta Pædiatrica **46**: 315. May 1957

ANNOUNCEMENTS

The Guigoz Fellowship for a Study on Nutrition

A Jury appointed by the International Children's Centre (ICC), Paris, will award *next June* the Guigoz fellowship for a study on nutrition, amounting to one million French francs. The fellowship was founded in 1856 by the Guigoz Company of Dietetic Products headquartered in Vuadens (Switzerland) to enable a nutritionist or a physician to devote one year to research work in Paris concerning feeding or nutrition of infants and children.

Applications for the 1957 fellowship must be filed not later than May 15, 1957. The applicants are required to send to the International Children's Centre, Château de Longchamp, Boulogne, Paris 16e:

(*a*) *a curriculum vitae* mentioning their work on biological and social problems, pertaining to the feeding or nutrition of infants and children;
(*b*) *a letter of introduction* from one of their Masters;
(*c*) *an outline of the studies* which they wish to engage in with the help of the Guigoz fellowship.

The applicants must have an adequate command of the French language.

At the end of the year covered by their fellowship, the fellow or fellows will be expected to send to the International Children's Centre *a scientific paper on the subject which they will have studied during the year.*

4th Meeting of the European Organization for Research on Fluorine and Dental Caries Prevention at Malmö, Sweden, June, 15th–17th 1957. Royal Dental School.

Information available from:

Prof. Syrrist, Malmö, Sweden, Royal Dental School,

and

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Dr. H. J. Schmidt, Stuttgart-Degerloch Germany, 5 Obere Weinsteige.

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Acta Pædiatrica 46: 316. May 1957

BOOK REVIEW

Günter Mackensen: **Die Psychomotorik blinder Kinder.**

Bücherei des Augenarztes. *Kl. Mtsbl. f. Augenh.k.* 1956, 26. Heft.

Die 48 Seiten lange Arbeit gibt eine Zusammenstellung über die Psychomotorik des blinden Kindes und beschreibt unter den angeführten, Kinder- und Augenärzten wohlbekannten Symptomen vor allem die motorischen wie Hypermotilität, die als rhythmische Körperbewegungen schon im 1. Lebensjahr beobachtet werden und oft im Alter von 4–5 Jahren völlig verschwinden. Ausserdem wird die charakteristische Mimik betont. Es handelt sich dabei um eine Ausdrucksarmut, die gelegentlich durch ein mehr oder weniger inadäquates Mienenspiel unterbrochen wird. Dabei ist für das blinde Kind die gegen die Augen gerichtete motorische Aktivität der Hände typisch, die in Form von Augenreiben usw. auftritt.

Schliesslich wird hervorgehoben, dass das blinde aber sonst gesunde Kind in seiner motorischen und psychischen Entwicklung nicht gehemmt ist. Die beobachte Retardierungen liessen sich später alle auf einen geringen Intelligenzgrad zurückführen.

B. Zetterström

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